Combating Diseases Associated with Poverty

Financing Strategies for Product Development and the Potential Role of Public-Private Partnerships

Principal Authors

Roy Widdus
Katherine White

A report on the status of the field based on a workshop of the same title organized by the Initiative on Public-Private Partnerships for Health

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In collaboration with:

Bill & Melinda Gates Foundation
Department for International Development (United Kingdom)
Rockefeller Foundation
Wellcome Trust

Held on 15–16 April 2004
at the Wellcome Trust, London, United Kingdom

Initiative on Public-Private Partnerships for Health

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Published by the Initiative on Public-Private Partnerships for Health, Global Forum for Health Research
November 2004
ISBN 2-940286-21-3

Designed by minimum graphics
Printed in Switzerland

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Dedication

This volume is dedicated to John La Montagne who committed his life to improving health, particularly for those disadvantaged by poverty. His memory will be long cherished by all who had the privilege of knowing him as a professional colleague and personal friend.

Acknowledgements

IPPPH would like to thank the following organizations for their financial, in-kind and intellectual support which made the workshop on *Combating Diseases Associated with Poverty: Financing Strategies for Product Development and the Potential Role of Public-Private Partnerships* and this book, in abridged and full versions, possible:

- Bill & Melinda Gates Foundation
- Department for International Development (United Kingdom)
- Global Forum for Health Research
- Rockefeller Foundation
- Wellcome Trust
- World Bank

Abbreviations and acronyms

ADIPs	Accelerated Development and Introduction Plans (GAVI)
AHRF	African HIV Research Forum
AMANET	African Malaria Network Trust
ARVs	antiretrovirals
BVGH	BIO Ventures for Global Health
CABs	Community Advisory Boards
CANs	development candidates
CDC	Centers for Disease Control and Prevention (United States)
CIDA	Canadian International Development Agency
CMM	Capital Markets Mechanisms working group (World Bank)
CONRAD/ CICCR	Contraceptive Research and Development Program/Consortium for Industrial Collaboration in Contraceptive Research
DAH	development assistance for health
DECs	disease-endemic countries
DFID	Department for International Development (United Kingdom)
DNDi	Drugs for Neglected Diseases *initiative*
DSMB	data safety and monitoring board
DSS	demographic surveillance systems
DTP	diphtheria-tetanus-pertussis
EDCTP	European and Developing Countries Clinical Trials Partnership
EMEA	European Medicines Evaluation Agency
EMVI	European Malaria Vaccine Initiative
EU	European Union
FDA	Food and Drug Administration (United States)
FIND	Foundation for Innovative New Diagnostics
FTE	full-time equivalent
GATBDD	Global Alliance for Tuberculosis Drug Development (TB Alliance)
GAVI	Global Alliance for Vaccines and Immunization
GCP	good clinical practice
GDP	gross domestic product
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
GFUNC	Gates Foundation/University of North Carolina Partnership for the Development of New Drugs
GMP	Global Microbicide Project
GSK	GlaxoSmithKline
HepB	hepatitis B
HHVI	Human Hookworm Vaccine Initiative
Hib	Haemophilus influenza type b
HRP	Human Reproductive Programme (WHO)
IAVI	International AIDS Vaccine Initiative
IBRD	International Bank for Reconstruction and Development (World Bank)
ICH	International Conference on Harmonization
IDA	International Development Association (World Bank)
IDRI	Infectious Disease Research Institute
IFC	International Finance Corporation (World Bank)
IFF	International Finance Facility
IFPMA	International Federation of Pharmaceutical Manufacturers Associations
IOWH	Institute for OneWorld Health

IP	intellectual property
IPM	International Partnership for Microbicides
IPR	intellectual property rights
IPPPH	Initiative on Public-Private Partnerships for Health
IRB	Institutional Review Board
JICA	Japanese International Cooperation Agency
LAPDAP	Lapdap Antimalarial Product Development
LMICs	low and middle income countries
MCA	Millennium Challenge Account (USA)
MDGs	Millennium Development Goals
MDP	Microbicides Development Programme
MHRA	British Medicines and Healthcare Products Regulatory Agency
MMV	Medicines for Malaria Venture
MSF	Médecins sans Frontières (Doctors without Borders)
MVI	Malaria Vaccine Initiative
MVP	Meningitis Vaccine Project at WHO/PATH
NEPAD	New Partnership for Africa's Development
NGO	non-governmental organization
NIH	National Institutes of Health (United States)
ODA	official development assistance
OPIC	Overseas Private Investment Corporation
PABIN	Pan-African Bioethics Initiative
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health
PD	product development
PDVI	Pediatric Dengue Vaccine Initiative
PEI	polio eradication initiative
PH-ROI	public health return on investment
PMA	portfolio management approach
PneumoADIP	Pneumococcal Vaccines Accelerated Development and Introduction Plan
PPPs	public-private partnerships
R–D–A	research–development–access
R&D	research and development
RFPs	requests for proposals
ROI	return on investment
RotaADIP	Rotavirus Vaccines Accelerated Development and Introduction Plan
SAAVI	South African AIDS Vaccine Initiative
SOPs	standard operating procedures
STIs	sexually transmitted infections
SVI	Albert B. Sabin Vaccine Institute
SWAps	sector-wide approaches
TAM	traditional African medicines
TB	tuberculosis
TBDI	Tuberculosis Diagnostics Initiative
TDR	UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
TPPs	target product profiles
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
USAIDMVDP	USAID's Malaria Vaccine Development Program
VF	Vaccine Fund
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

Preface

Public-private partnerships for health product development: Why a critical review now?

In the mid-1990s, some fundamentally different ventures began to emerge addressing the development of products for combating diseases associated with poverty. These have come to be known as public-private partnerships (PPPs) although some prefer other descriptive phrases. Collaboration on an ad hoc basis and around individual candidate projects had, however, occurred previously between public sector agencies and private sector pharmaceutical companies.

What distinguishes these new ventures is that they take as their starting point not a ('favourite') specific candidate product, but a survey of the field and then promote the parallel development of a range of different candidate products (a 'portfolio'). Management of a portfolio, borrowed from the pharmaceutical and venture capital fields, is designed to manage the risk of failure accompanying any individual project. Prior to the mid-1990s, no public-interest venture engaged in product development had articulated 'portfolio management' as a conscious strategy. Some of the product development ventures considered at the 15–16 April 2004 meeting convened by the Initiative on Public-Private Partnerships for Health (IPPPH) in London have, as yet, only small portfolios. However, the older ventures have at least five to six years of operational experience and sizeable portfolios, some over 25 projects.

The emergence of these new ventures was initially fostered by the Rockefeller Foundation and subsequently, around the turn of the millennium, by substantial funding from the Bill & Melinda Gates Foundation. Their number is presently approaching 20. More new ventures to address currently unmet needs (for example, for control of noncommunicable diseases) may possibly emerge.

While they draw upon skills and procedures that are well established in the commercial sphere, these product development PPPs are essentially 'social experiments'. 'Best practices', proven by the delivery of products, are not yet available. The desire to know how to assess the added value of these ventures, as well as 'partnership proliferation', are high on the agenda of concerns for both existing and prospective funders such as bilateral aid agencies. These funders also need to know the scale of future resources needed.

These same funders and many other entities, including the World Bank, UNDP, WHO and developing country governments, are currently seeking ways to achieve the UN Millennium Development Goals (MDGs), adopted in September 2000, and other internationally agreed targets.[1] Of these MDGs, half relate directly or indirectly to health, and one specifically calls for a partnership with the pharmaceutical industry to provide access to affordable essential medicines.[2]

At present, however, it seems very unlikely that the MDG targets for 2015, and particularly the health-related ones, will be achieved in most of the poorer countries. Unfortunately, the debate on achieving the MDG targets has not recognized that the array of 'tools' available to meet the international targets on child mortality, HIV/AIDS, tuberculosis (TB) and malaria are inadequate for the poorer countries. Major

[1] The UN General Assembly Special Session on HIV/AIDS Declaration of Commitment: Three million people – 2 million in Africa – receiving treatment by the end of 2005.

The Abuja targets for malaria in Africa: By 2005, ensure 60% of those with malaria have access to appropriate treatment.

The Amsterdam target for tuberculosis: By 2005, 70% of people with infectious TB will be diagnosed and 85% cured.

[2] Goal 8, Target 17, Indicator 46.

causes of child mortality, such as pneumococcal pneumonia and rotavirus diarrhoea, lack preventive vaccines. There is no vaccine or microbicide to prevent HIV infection, no vaccine for malaria and no vaccine to prevent the majority of TB cases (in adults). Existing diagnostic tools or therapies for most diseases associated with poverty are old and/or difficult to use. Most drugs are threatened by increasing resistance.

Given this situation, the Initiative on Public-Private Partnerships for Health concluded that taking stock of experience to date would help a range of constituencies to maximize the value of their future investments of money and effort in product development. Partnerships, we hope, can learn from each other; existing donors can compare and contrast practice for adjusting their support; and prospective funders can see what types of ventures most closely align with their missions. Finally, a new dimension can be added to the debates about achieving the MDGs, namely improving the array of tools that can facilitate their achievement.

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Public-private partnerships to combat health problems associated with poverty

Message from the World Health Organization

The mission of the World Health Organization (WHO) includes fostering research and product development to address the health problems that burden its Member States, particularly the poorer ones.

Significant contributions to this goal have been made by various WHO implemented programmes, such as the World Bank/UNDP/WHO Special Programme for Research and Training in Tropical Diseases (TDR), the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research in Training in Human Reproduction (HRP), and more recently the Initiative on Vaccine Research. We anticipate a continuing role for these programmes.

Over the last few years, WHO has also participated in the development and launch of some new not-for-profit ventures that complement WHO core role. These include, the Medicines for Malaria Venture, the Global Alliance for Tuberculosis Drug Development, and the Foundation for Innovative New Diagnosis, as well as broader coordination mechanisms, like the Global Alliance for Vaccine and Immunization and the Stop TB Partnership.

Such collaborations strengthen the overall global movement for better health. WHO welcomes these and the other new ventures addressing neglected diseases. They support our shared goal, and WHO's underlying mission, to ultimately break the deadly cycle of diseases and poverty in which – even in today's globalizing world – too many individuals are still trapped.

LEE Jong-wook
Director-General
World Health Organization

Message from the International Federation of Pharmaceutical Manufacturers Associations

For decades, the research-based pharmaceutical industry has fostered the development of new medicines and vaccines that have saved lives and improved the health of millions of people around the world. Not only have these innovations helped the poor by dealing with major causes of the global burden of disease, but the pharmaceutical industry has also developed products needed to combat conditions that affect primarily the health of poor populations.

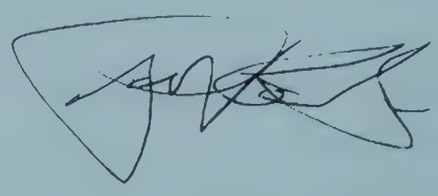
Some commentators have expressed misgivings that as global competition among companies increased, there would be less attention to the needs of the poor, particularly as the costs of bringing new innovative products to the market increased. Fortunately, all major R&D-based companies continue to address the needs of poorer populations through a variety of mechanisms. These include research collaborations; donation programmes or differential pricing policies for poorer populations; special packaging and formulations; initiatives to assure quality and discourage counterfeit medicines; and educational, training and other programmes to strengthen the infrastructure and human resource capacity for the delivery of healthcare services.

The accumulated expertise and experience represented in research-based pharmaceutical companies is

a major resource for global health. It would be wasteful to duplicate this or not to recruit it to social purposes, such as those represented by the Millennium Development Goals. Linking private sector expertise with public sector goals to combat global health problems obviously makes sense.

R&D-based companies welcome the emerging array of new ventures – so-called public-private partnerships – specifically addressing diseases associated with poverty. These ventures facilitate the processes by which industry can utilize its unique strengths – expertise for innovative product development – to address the needs of the poor. These new ventures also represent disciplined ways of working toward success in a timely manner, approaches familiar to industry and necessary for the efficient and effective use of everyone's resources.

IFPMA, the official representative of the pharmaceutical industry's innovator companies worldwide, welcomes the opportunities that these new ventures create to address the critical needs of those who still suffer disproportionately from the health problems associated with poverty. Investing in health is the surest way to find the path to economic development and greater wealth. Public-private partnerships have an important role to play in achieving that worthy and ambitious goal.



Raymond V. Gilmartin
Chairman, President and
Chief Executive Officer, Merck & Co., Inc.
President, International Federation of Pharmaceutical
Manufacturers Associations, 2002–2004

Executive summary

Background

In the mid-1990s, a new group of not-for-profit ventures addressing the development of health products for combating diseases associated with poverty began to emerge. This phenomenon resulted from trends in the late 20th century including awareness of disease burden distribution, changing pharmaceutical industry economics, and the emergence of 'champions' for tackling specific health inequities. To mitigate risks arising from individual project failures, these ventures adopt the pharmaceutical industry approach of developing various candidate products simultaneously and recruit, to varying degrees, industry collaboration in their efforts. Hence, they have become known as 'public-private partnerships' (PPPs), although some prefer other descriptive phrases. About 20 PPPs now exist, some relatively new with small portfolios; others having over six years' experience and managing sizeable portfolios of more than 25 products.

While they have underlying similarities, these ventures also vary, particularly owing to factors arising from their choice of disease target (HIV/AIDS, malaria, tuberculosis or other) and product focus (drugs, vaccines, diagnostics, microbicides or other health product).

Workshop summary

On 15–16 April 2004, a workshop entitled *Combating Diseases Associated with Poverty: Financing Strategies for Product Development and the Potential Role of Public-Private Partnerships* was organized by the Initiative on Public-Private Partnerships for Health (IPPPH), part of the Global Forum for Health Research, in collaboration with the Bill & Melinda Gates Foundation, the UK Department for International Development, the Rockefeller Foundation and the Wellcome Trust which hosted the workshop at their London headquarters.

The workshop was organized around five objectives:

- Provide background on the emergence and operations of these ventures.
- Consider how product development (PD) PPPs and other players operate and interact.
- Assess the current and future financial needs of PD PPPs.
- Assess if innovative financing options for diseases of the poor exist.
- Identify questions and issues requiring further attention and study.

During the workshop and an associated consultation among existing PD PPP funders, it became clear that PD PPPs could be considered a coherent grouping or field albeit with differences around individual ventures arising mostly from their choice of disease and product focus which significantly affects the context in which they operate.

The main themes in the discussions were:

- Agreement, generally, that the PD PPP model (albeit with variations) was a sound and cost-effective approach to product development for diseases associated with poverty, probably the best that could be currently identified.
- Interfaces with other organizations in the research–development–access (R–D–A) continuum were critical and a major management challenge for PD PPPs. This encompassed both upstream interfaces with basic research, downstream interfaces with potential delivery systems, effective management of interfaces with private sector collaborators and 'contractees' in the specific steps of product development, and links with

researchers and policy-makers in disease-endemic countries (DECs).

- Effective portfolio management is a critical factor allowing PD PPPs (and donors) to spread risks of individual project failure, thus favouring ultimate success. In addition, the technical expertise of PD PPP staff and Scientific Advisory Boards provided added-value to funders who may not have, or wish to have, the in-house scientific capacity to manage product development themselves.
- Consideration was needed of the activities required to achieve optimal access for the poorer populations in need of the anticipated health products. Identifying necessary actions becomes more important where delivery systems are not easy to identify or function poorly. The PD PPPs may be in a good position to advocate for the necessary actions but responsibility for implementation probably more appropriately rests with other players.
- The financing required for product development will vary given the disease/product choices of the PD PPP. Based on estimates of funds committed by early 2003, and cost estimates for the portfolio of products underway, the financing shortfall through 2007 for major PD PPPs appears to be at least US$ 1.2 billion and possibly over US$ 2.2 billion, depending on assumptions. Techniques for assessing the amounts necessary need to be refined. Nonetheless, PD PPP projections and estimates from independent sources prepared for the workshop using industry costs as reference suggest a large shortfall in the near term. This shortfall exists, even for the best-funded PD PPPs, as well as across the field. Credible certainty about financing can affect the level of collaboration from industry.
- Judging 'success' is important to funders and requires the development of comparative performance measures.
- Communication and coordination among all players is critical to the field, as cooperation of so many players (funders, PPPs, industry, DECs, etc.) is required to ensure progress of candidate products along the R–D–A continuum. Current levels are probably suboptimal, but mechanisms need to be 'light' as most players are already stressed by current obligations.

Areas for future attention

Participants did not prioritize conclusions and recommendations at the workshop. However, subsequent consultation among the meeting chairs and session co-chairs, funders and PD PPPs identified some consensus on areas for future attention:

- Development of common performance measures.
- Coordination of clinical trial capacity development.
- Harnessing the potential of disease-endemic countries.
- Ensuring financial sustainability of the PD PPPs.
- Communication and coordination.
- Fully recruiting potential industry contributions.

These are discussed further in the report from the workshop, along with possible approaches to moving forward. First, however, some historical context is provided, for readers new to this field.

Historical context

Why public-private partnerships for product development emerged and how?

Roy Widdus

The reason that a wave of new multi-candidates/portfolio-based ventures for product development to combat 'diseases predominantly associated with poverty'[1] arose in the late 1990s has not been subject to extensive examination. Analysis of the emergence of individual ventures does not help with our general understanding of this phenomenon, as such analysis often tends to focus on the disease burden that a particular venture hopes to alleviate and the scientific prospects for new products. As analysis shifts to changes in the environment in which the ventures emerged, it becomes somewhat more speculative but worth attempting. Trends in the late 20th century that probably created an environment conducive to the burgeoning of these new ventures are discussed below. Such an analysis, however, cannot define the relative contribution of different factors in their emergence.

Trends in the late 20th century conducive to emergence of PD PPPs

The last two decades of the 20th century saw a number of trends that created a fertile environment for the emergence of new ventures against diseases associated with poverty. These are briefly described below.

Systematic analysis of the global burden of disease highlighted diseases associated with poverty and deficiencies in tools to combat them

Work on the rich-poor health inequalities[2] and global burden of disease[3] led to wider recognition that for the world's poorest, infectious diseases still currently represent the major differential cause of premature death and disability.

Analysis further identified the deficiencies in the tools available to tackle many of these diseases.[4] Such deficiencies exist both in terms of the array of tools necessary for effective control (preventive, diagnostic, and therapeutic) and in their appropriateness for use in resource-constrained developing country settings.[5]

Table 1 shows recent WHO estimates of the mortality and disease burden arising from selected conditions that disproportionately affect poor populations. In many cases specific disease burden estimates have been developed for the major contributors to disease burden within broad categories of health problems. For example, rotavirus within diarrhoeal diseases or pneumococcal pneumonia within lower respiratory infections, respectively cause an estimated 500,000 to 800,000 and 800,000 to 1 million deaths annually.[6,7] While Africa represents around 11% of the global population, it accounts for around 55% of the deaths from infectious and parasitic diseases. Tropical diseases, which particularly afflict the poor, represent a signifi-

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[1] Sometimes termed 'neglected diseases', although some, such as HIV/AIDS, receive considerable funding overall.

[2] World Bank. 1993. *World Development Report: Investing in Health*. World Bank. 320 pp.

[3] Murray CL, Lopez AD. 1996. *The Global Burden of Disease*. World Health Organization and Harvard University Press. 990 pp.

[4] Ad Hoc Committee on Health Research. 1996. *Investing in Health Research*. World Health Organization. 278 pp.

[5] Preventive vaccines are lacking (HIV/AIDS, malaria) or poorly effective in adults (TB) for the major killers. Easy to use, affordable drugs are lacking (HIV/AIDS) or are threatened by resistance (malaria, TB), and diagnostic tools are outdated (TB) or lacking (malaria). For the diseases predominantly limited to tropical settings (trypanosomiasis, leishmaniasis), similar problems can be outlined along with few currently available therapies, which are mostly unsatisfactory due to toxicity or difficulty of use. For global pathogens that mainly kill those in developing countries, e.g. rotavirus and pneumococcus, vaccines are only just now becoming available and introduction needs to be accelerated.

[6] See: www.rotavirusvaccine.org.

[7] See: www.preventpneumo.org.

Table 1. Estimates of deaths and burden of disease by various causes for 2002

	Deaths (000)	(%)	DALYs (000)	(%)
Total	**57,029**	**100**	**1,490,126**	**100**
Communicable diseases, maternal and perinatal conditions and nutritional deficiencies	18,324	32.0	610,319	41.0
Infectious and parasitic diseases	10,904	19.1	350,333	23.5
Tuberculosis	1,566	2.7	34,736	2.3
HIV/AIDS	2,777	4.9	84,458	5.7
Diarrhoeal diseases	1,798	3.2	61,966	4.2
Childhood diseases (vaccine preventable)	1,124	2.0	41,480	2.8
Malaria	1,272	2.2	46,486	3.1
Tropical diseases	129	0.2	12,245	0.8
Trypanosomiasis	48	0.1	1,525	0.1
Chagas disease	14	0.0	667	0.0
Schistosomiasis	15	0.0	1,702	0.1
Leishmaniasis	51	0.1	2,090	0.1
Lymphatic filariasis	0	0.0	5,777	0.4
Onchocerciasis	0	0.0	484	0.0
Dengue	19	0.0	616	0.0
Japanese encephalitis	14	0.0	709	0.0
Lower respiratory infections	3,884	6.8	91,374	6.1
Nutritional deficiencies	485	0.9	34,417	2.3
Noncommunicable diseases	33,537	58.8	697,815	46.8
Injuries	5,168	9.1	181,991	12.2

Source: *World Health Report 2004*. World Health Organization, Geneva, Switzerland.

cant debilitating burden of disability (as measured in disability-adjusted life years [DALYs]) even though in overall terms they cause relatively few deaths.

Pharmaceutical companies faced increasing R&D costs, consolidation and greater competitive pressures, increasing their aversion to commercially risky or unattractive projects

It is generally accepted that in the latter decades of the 20th century, the R&D-based pharmaceutical industry faced rising costs for bringing each new product to the market (even if the exact costs are debated).

One response to this situation was mergers and acquisitions creating a relatively small number of 'mega-companies', competing intensively for shareholder investment and each seeking 'blockbuster' projects capable of generating annual revenues in the multi-million, preferably billion dollar range. Some sources suggest that as of 1997, most major pharmaceutical companies would have no interest in products with anticipated annual revenues of less than US$ 300,000,[1] a level higher than expected for many of the products needed to tackle diseases of poverty.

All these trends rendered it increasingly unlikely that companies alone would invest their own R&D resources in products to combat diseases predominantly affecting poor populations.[2]

[1] Mercer Management Consulting. 1997. Report prepared for the Children's Vaccine Initiative.

[2] Activist calls for greater 'corporate social responsibility' did not emerge until around 2000, and – in reality – probably play less of a role in overall decision-making (by companies and investors) than profitability.

Vaccines are increasingly 'orphan' products, despite their public health importance in developing countries

Preventive vaccines continued to comprise a smaller fraction of the total pharmaceutical market, and most major companies focused on a selected rather than a comprehensive range of candidates in development – overwhelmingly for affluent markets.

Vaccines, as compared to drugs, are relatively unattractive commercial products. This results from a number of factors:

- Vaccine development requires major but risky investment in product-specific manufacturing plant (for clinical trials) before the certainty of a marketable product (and revenues) is established. (Drug manufacturing on the other hand can be scaled up after efficacy is established.)
- Purchasers of vaccines (generally governments) are more price-sensitive and able to negotiate lower prices (hence lower margins) than patients seeking (drug-based) therapies.
- The target population for vaccines – healthy individuals – requires close to absolute safety and side-effects discovered post-marketing (e.g., Wyeth's rotavirus vaccine) can cause expensive product withdrawal.

For vaccines against the major three poverty-related diseases (HIV/AIDS, TB and malaria), the scientific pathways to a successful product are uncertain, but will be relatively expensive, since likely efficacy must be established in large human trials.

Understandably, this situation leads to lower interest by major companies in vaccine development in general and to even lower interest in vaccines with predominant demand in poorer populations.

The HIV/AIDS pandemic draws global attention to the need for greater action on health needs of low- and middle-income countries

The increasing impact of the HIV/AIDS pandemic on poor populations, especially in sub-Saharan Africa, was known to international public health specialists from the mid-1980s onwards. However, most 'activism' in the 1980s and early 1990s was confined to affluent countries and directed principally to the needs of affected individuals in such settings.

In the early to mid-1990s, the availability of multidrug, antiretroviral (ARV) therapy led to the possibility of extending the lives of people with HIV/AIDS by a significant degree, albeit at high cost.

With the wide availability of ARVs in industrialized countries, the difference in prospects for poor, as compared to rich, patients led to a new wave and direction for HIV/AIDS activism. Starting in the mid-1990s, calls to make treatments for HIV/AIDS more widely available, and at much lower price, in developing countries increased substantially, and from many different types of organizations.

Those undertaking advocacy and 'activism' for better access of those in developing countries to HIV/AIDS treatments also promoted, to varying degrees, greater awareness of the need to improve access to treatments (or prevention) for other diseases, such as malaria, tuberculosis and trypanosomiasis.

This spillover effect raised general awareness of diseases associated with poverty and the need to ensure better tools for their control. The general climate of opinion shifted towards higher expectations that R&D-based pharmaceutical companies would do something about developing country health needs.

Public health and public interest organizations improve their understanding of industry motivations and product development expertise

An additional factor that may have played a role in the emergence of the new PPP ventures is better recognition in public health and public interest organizations of the value of approaches used in industry and better understanding of its underlying economics and motivations. While no systematic study has been conducted, a number of anecdotal examples can be found that suggest that this may have played some role in new venture creation.

From the late 1980s to the mid-1990s, the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) increasingly incorporated explicitly the aim of product development. In this period, staff with industry experience were brought into the programme in significant numbers and positions for the first time. These included the architects of the Medicines for Malaria Venture (MMV, see below).

From the early 1990, WHO and UNICEF, under the stimulation of the Children's Vaccine Initiative

(CVI), undertook studies on the economics of commercial vaccine supply for developing countries and on vaccine production. These studies and the general increased interaction with industry under the CVI probably led to better recognition of industry approaches and motivations. Certainly, the architects of the process that led to IAVI (described below) were familiar with these lessons.

This better understanding of industries' approach to product development on the part of public health or public interest (philanthropic) organizations, in and of itself, was not probably sufficient to trigger the emergence of PD PPPs.

It is likely that those with industry experience in public sector organizations (such as WHO) and those in private philanthropic foundations wishing to 'borrow' from industry to achieve success recognized that what was necessary could not be accomplished without a flexible new 'hybrid' approach.

The emergence of discrete ventures dedicated to product development for neglected diseases

Adoption of the multi-candidate/portfolio approach by ventures committed to global public health (as a means of enhancing likely success) appears to have occurred in various independent circumstances particularly in the mid- to late 1990s. Each represents recognition of the necessity for effective public-private collaboration, from different starting points.

Antecedents of the not-for-profit product development ventures in infectious diseases

Antecedents of the portfolio-based, not-for-profit infectious disease PD PPPs emerging in the mid-1990s can be seen in some research programmes on contraception. The principal example is the Contraceptive Research and Development Program (CONRAD), which was established by the US Agency for International Development in 1986 at the Eastern Virginia Medical School to expedite new contraceptive development. CONRAD conducts and funds activities across multiple R&D projects for contraceptives and, nowadays, microbicides.

At the same time as IAVI and MMV were emerging, CONRAD and its supporters developed a Consortium for Industrial Collaboration in Contraceptive Research (CICCR), formally established in 1995. Based on the belief that risk sharing in the early stages of the product development process could attract industry's investment in much needed contraceptive and microbicide research, CICCR was set up to:

- identify leads under investigation in not-for-profit institutions, in both developed and developing countries, that could result in new contraceptive methods in the priority areas specified by the women-centred agenda of the 1994 Cairo conference; and
- encourage industry to collaborate with CICCR by providing support to investigators at not-for-profit institutions.

Even though there is no commercially marketed product as yet, the industrial partnerships established have enabled CONRAD to take a product into late-stage clinical trials. The partnerships have also resulted in developing a knowledge base at CONRAD applicable to other candidate products in the pipeline. These ventures thus adopted elements of the approach that was also embraced independently by the ventures described below.

The emergence of the first PD PPP for vaccine development: International AIDS Vaccine Initiative

Various discussions occurred in the late 1980s and early 1990s regarding the need for expanded efforts on vaccines to combat HIV/AIDS. These took place in both formal meetings convened by the US Institute of Medicine and the World Health Organization, and informally among an interested group in association with international meetings on AIDS, such as that in Berlin in 1993, with an increasing focus on the needs of less developed countries. Individuals involved in these discussions included José Esparza, who continued to manage WHO – and subsequently UNAIDS – activities on HIV/AIDS vaccines; Don Francis, who founded VaxGen Inc., to test an early candidate, AIDSVAX; and Seth Berkley, who took forward the approach outlined below.

On 7–11 March 1994, the Rockefeller Foundation convened at its Bellagio Conference Facility a meeting entitled *Accelerating the development of preventive HIV vaccines for the world*. The Rockefeller Foundation has a long history in philanthropy for global public health and the meeting's principal architect was Seth Berkley,

a public health epidemiologist with experience of the early HIV/AIDS epidemic in Uganda, then working at the Foundation.

The meeting's 24 participants concluded, *inter alia*, that:

> "...the development and testing of multiple empirical approaches in a parallel fashion rather than sequentially, will be a faster route to the development of safe, effective and inexpensive vaccines appropriate for widespread [i.e., developing country] use, ...but one which industry alone was unlikely to take because of lack of commercial incentives for the developing country market."

They additionally concluded that:

> "Success in developing an HIV vaccine will require the involvement of both public and private sectors".

but stressed that, given the commercially unattractive developing country market:

> "Positive steps will have to be taken if pharmaceutical and biotechnology companies are to be encouraged to commit more fully their expertise, experience and resources to the development of a preventive HIV vaccine."

While the meeting was exploratory, it concluded that a new initiative was needed and laid out a set of characteristics and activities, which would be necessary for the mission to be pursued effectively.[1]

Further meetings were sponsored by the Rockefeller Foundation, under the guidance of Seth Berkley, on a scientific agenda[2] (also co-sponsored by the Foundation Mérieux) and on financial and structural issues[3] which laid the groundwork for the International AIDS Vaccine Initiative (IAVI).

IAVI became an independent legal entity in 1996. Significantly the Bellagio participants concluded:

> "Experience with drugs and vaccines for other diseases suggests that measures will need to be taken to ensure that once a vaccine is developed it is accessible to those at risk of infection throughout the world with the least possible delay."

This statement presaged a major component of IAVI's activities. Subsequent to initiation of its product development activities (see [4,5]), it launched efforts in addressing 'access'.[6]

IAVI thus originated in the recognition by the private philanthropic sector of a global public health need. Its adoption of a 'portfolio' approach was driven mostly by the realization – independent of industry – that this maximized the chances of getting to a useful product with the least delays. For the most part, securing industry engagement, in projects or to the overall venture, was left to the new entity, post-creation. Industry expertise was recognized as necessary, but so was the need to go beyond industry's usual role, into advocacy and access for poor populations to anticipated products.

Medicines for Malaria Venture: The first PD PPP for drug development

Shortly after the Rockefeller Foundation initiated the process that led to IAVI, staff within the UNDP/World Bank/WHO began discussions that ultimately led to the creation of the Medicines for Malaria Venture (MMV). These discussions were initiated by two individuals, Win Gutteridge and Robert Ridley, who knew product development and the benefits of a portfolio approach in increasing the probability of success from their prior experience in the pharmaceutical industry.[7] When working with Wellcome and Glaxo-Wellcome, Gutteridge had written position papers highlighting the need for special new efforts to ensure continued attention to the need for drug development for 'tropical diseases including malaria'.

The major issues that arose during discussions about revitalizing anti-malarial drug development to meet

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[1] Rockefeller Foundation. 1994. *Summary report and recommendations of an international meeting: HIV vaccines – Accelerating the development of preventive HIV vaccines for the world.* 7–11 March 1994, Bellagio, Italy. 27 pp.

[2] Rockefeller Foundation. 1995. *Summary report and recommendation of an international ad hoc scientific committee.* 27–28 October 1994, Le Val de Grâce, Paris, France. 24 pp.

[3] Rockefeller Foundation. 1995. *Summary report and recommendations of an international meeting: Financial and structural issues.* 17 August 1995, New York. 16 pp.

[4] International AIDS Vaccine Initiative. *Scientific Blueprint – 1998.* 22pp

[5] International AIDS Vaccine Initiative. *Scientific Blueprint – 2000.* 29pp

[6] International AIDS Vaccine Initiative. 2000. *AIDS Vaccines for the World: Preparing now to assure access.* 55 pp

[7] Ridley RG, Gutteridge WE, Currat LE. 1999. Unpublished manuscript presented at the 3rd Forum of the Global Forum for Health Research, Geneva. *New medicines for malaria: A case study of the establishment of a public/private sector partnership.*

developing country needs were those relating to industry engagement and the nature of the venture that would be able most effectively to catalyse new product development. Industry endorsement and engagement was actively sought and eventually negotiated through interactions with major companies facilitated by the International Federation of Pharmaceutical Manufacturer's Associations. An independent, not-for-profit legal status was eventually accepted as the most appropriate structural arrangement. The Rockefeller Foundation funded the first 'business plan' for a PD PPP,[1] which reportedly helped increase credibility of the new venture with prospective funders.[2] Various other groups, including the Global Forum for Health Research, facilitated the creation and early operations of the nascent venture. MMV was established under Swiss law as a foundation in 1999.

Thus, the first PD PPP for drug development was championed by individuals convinced of the need to apply industry methods (in portfolio management) to public health goals, and who saw full industry engagement as essential from the outset.

These examples illustrate a theme recurring in review of PD PPPs, namely, underlying similarities in objectives but differences in the process through which they are attained.

Role of Foundations in nurturing and expanding the field of product development partnerships

Two foundations have been instrumental in the start-up and funding of various PD PPPs. These are the Rockefeller Foundation through their Health Equity Program and the Bill & Melinda Gates Foundation (B&MGF), whose greatly expanded endowment in 1998/99 allowed it to become a major investor in combating diseases associated with poverty.

Rockefeller's involvement started with the formation of IAVI. When IAVI was founded, Seth Berkley, then at Rockefeller, left to lead the organization. Following Berkley's departure, the new leadership in the health area at the Rockefeller Foundation (Lincoln Chen, Tim Evans and Ariel Pablos-Mendez) continued its tradition of interest in application of scientific research for control of neglected diseases. Fostering its application to specific diseases became a component of the Foundation's programme in health equity.

In addition to IAVI, where it played a pivotal role, and MMV, where it contributed to a new dimension (the business plan), the Rockefeller Foundation has fostered the creation of a number of other PD PPPs in the last few years.

Typically, this has been through funding and organizing a broad consensus development process, which sometimes lasts up to two years. This process has successively included specific studies that are coming to be recognized as essential for a comprehensive approach: a scientific situation assessment and plan; a pharmaco-economic assessment (of need, market, costs and economics); and an assessment of access issues.

Ventures launched following 'incubation' by the Rockefeller Foundation (other than IAVI and MMV) include:

- Global Alliance for Tuberculosis Drug Development (TB Alliance) (2000), which also benefited at its launch from endorsement and significant 'seed' funding from the B&MGF
- International Partnership for Microbicides (IPM) (early 2001)
- Pediatric Dengue Vaccine Initiative (PDVI) (2001)

In late 1999, the Rockefeller Foundation suggested that the Global Forum for Health Research create an initiative to monitor the various emerging PPPs and identify what appeared to be predictors of success. This suggestion led to the creation of the Initiative on Public-Private Partnerships for Health (IPPPH) under the Forum's legal auspices in 2000.

Since the inception of its global health programme, the Bill & Melinda Gates Foundation has consistently devoted a major portion of its grant-making to portfolio-based public-private partnerships for product development.

The B&MGF provided a significant infusion of resources to already established PD PPPs (IAVI, MMV, Sequella Global TB Vaccine Foundation [see also discussion of Sequella/Aeras below] and the Tuberculosis Diagnostics Initiative [TBDI]) at the time of the endowment expansion. Other PD PPPs were in an independent process of formation at this time or later and also benefited (for example, the TB Alliance, IOWH, IPM and PDVI).

[1] Prepared by the Boston Consulting Group. 2000.

[2] Chris Hentschel. 2004. Medicines for Malaria Venture. Personal communication.

In other cases, ventures were relaunched (FIND, as it evolved from TBDI) or launched exclusively (HHVI) or overwhelmingly (MVI) with B&MGF funding.

Unlike those ventures 'incubated' by the Rockefeller Foundation, most ventures that owe their origins predominantly to the Bill & Melinda Gates Foundation tend not to have undertaken a wide consultation and consensus development process prior to the start of operations. Their support base, at least in financial terms, remains very narrow.

The B&MGF has significantly funded certain single candidate product development ventures, including the Meningitis Vaccine Project at PATH.

It should be noted that in addition to PD PPPs, the Bill & Melinda Gates Foundation has also funded other ventures and activities addressing major health problems of the poor, including micronutrient malnutrition (Global Alliance for Improved Nutrition), reproductive health, and infectious diseases control.

Emergence of other PD PPPs

A number of the PD PPPs addressed in this book and the prior meeting originated through processes different to those described above. For example, the Institute for OneWorld Health was launched independently from the foundations noted above. Some evolved into their current model from earlier, significantly different, incarnations.

The current Foundation for Innovative New Diagnostics (FIND), which was established as a Swiss foundation in 2003, is in the early stages of assembling a portfolio of candidate diagnostic products. However, its antecedents date back to 1996, first as a very small development programme for tuberculosis diagnostics within the World Bank/UNDP/WHO TDR and later with the same mission and hosted status but with massively increased funding (in 1998) from the Bill & Melinda Gates Foundation. Its current status and broader mission resulted from discussions in 2002/03 regarding the best status to enable the fullest possible range of flexible, timely operations and interactions with commercial organizations.

Originally, the Sequella Global Tuberculosis Vaccine Foundation was created in loose association with a small biotech company. Its early orientation was towards strengthening capacity to enable other organizations to develop and test products. In 1999, the B&MGF provided US$ 25 million for these activities. In 2003, the organization adopted a new name (Aeras) and reoriented its strategy to encompass product development *per se* and in 2004 received a further US$ 82.9 million for its activities.

The processes for creating PD PPPs evolve as do the ventures themselves

Champions appear to play a significant role in the emergence of PD PPPs but as the field develops, other elements seem to be emerging as reasonable predictors of a successful launch with broad-based support. These include:

- an inclusive process for achieving consensus on the mission of a new venture and the activities most needed;
- a scientific review/blueprint;
- a pharmaco-economic study, to define the need and possible market;
- a business case/business plan, which describes the problem that the venture will address, the activities needed to accomplish the goal, how they will be undertaken, and the resources required to do them; and in some cases,
- an 'access' plan, particularly in those cases where the path to use is otherwise unclear, since no delivery system is immediately apparent.

Some champions, or organizations, forgo these steps and move straight to creating a new venture and hoping to garner broader support in due course. These tend to start their operations with a narrow base of funders (sometimes only one). To date, most ventures started in this manner have remained with a narrow financial base.

Product development partnerships examined at the IPPPH London meeting[1]

A widely accepted and consistently used definition of 'public-private partnerships for health' remains elusive. The term is sometimes used (perhaps inappropriately)

[1] This listing, and the IPPPH London meeting of 15–16 April 2004, focused on ventures addressing infectious diseases. The Contraceptive Research and Development Program and its Consortium for Industrial Collaboration in Contraceptive Research (CONRAD/CICCR) use a portfolio approach to new contraceptive development. See Partnerships Database: www.ippph.org

to cover private sector delivery of health services, the rules for which are actually solely government controlled.

One proposed working definition includes "combining different skills, expertise and other resources – ideally in a framework of defined responsibilities, roles, accountability, and transparency – to achieve a common goal that is unattainable by independent action".[1] This definition still includes a variety of mechanisms and participants, and covers many public-private collaborations targeting product development in different ways.

As alluded to in the Preface, public-private collaboration for development of products to combat 'neglected diseases' did not arise *de novo* in the mid- to late 1990s. The defining feature of the new ventures which started to emerge at that time is that they elect to foster the simultaneous development of a number of candidate products portfolios, rather than starting with any specific ('favourite') project. This category was considered to include the following ventures:

HIV/AIDS

International AIDS Vaccine Initiative (IAVI)
South African AIDS Vaccine Initiative (SAAVI)
Global Microbicide Project (GMP)
International Partnership for Microbicides (IPM)
Microbicide Development Project (MDP)

Malaria

Medicines for Malaria Venture (MMV)
Malaria Vaccine Initiative (MVI)
European Malaria Vaccine Initiative (EMVI)

Tuberculosis

Global Alliance for Tuberculosis Drug Development (TB Alliance)
Aeras Global Tuberculosis Vaccine Foundation (Aeras)
Foundation for Innovative New Diagnostics (FIND)

Other 'neglected infectious diseases'

Drugs for Neglected Diseases *initiative* (DNDi)
Institute for OneWorld Health (IOWH)
Pediatric Dengue Vaccine Initiative (PDVI)
Human Hookworm Vaccine Initiative (HHVI)
Rotavirus Vaccine Accelerated Development and Introduction Plan (RotaADIP)
Pneumococcal Vaccine Accelerated Development and Introduction Plan (PneumoADIP)

This listing may be incomplete due to ventures using a portfolio approach on which IPPPH does not as yet have adequate information. At the time of the London meeting, BIO Ventures for Global Health (BVGH) was emerging; it is now described in Annex 3a, but is not included in the analyses conducted for the meeting such as that by Sander and Widdus (Annex 9b).

Information on the various types of public-private partnerships for health is provided in a background paper prepared for the meeting, which also includes specific information on these organizations.[2]

A current snapshot of the PD PPPs addressed

Similarities among PD PPPs

Those closely associated with individual ventures (and charged with selling their uniqueness to funders) will tend to emphasize differences among the crop of new product development ventures. However, impartial observation can identify significant common, underlying characteristics across this group of new ventures:

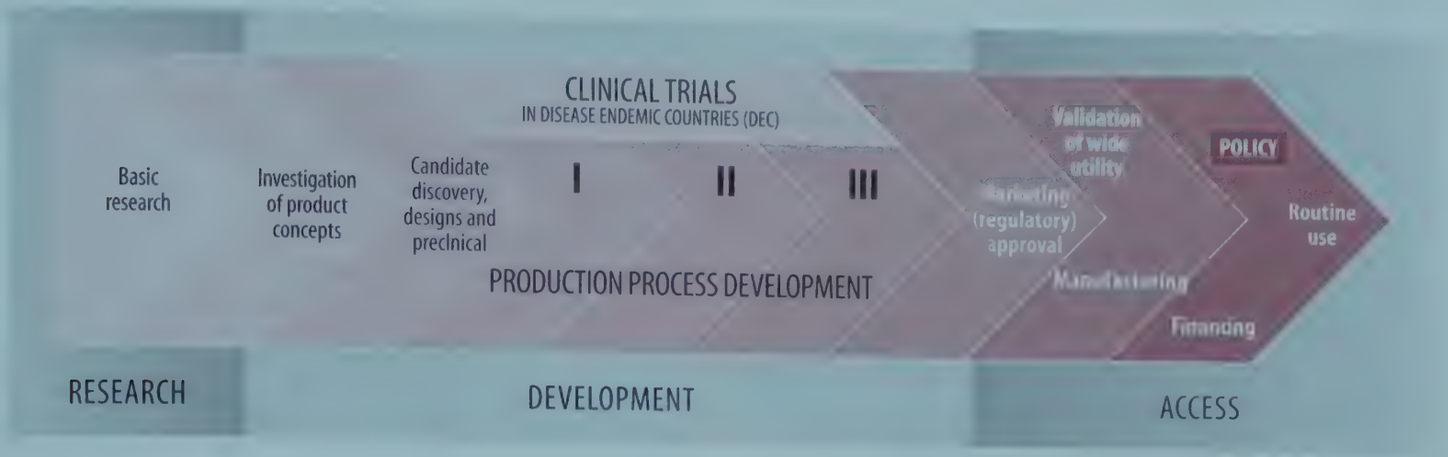
- They use some private sector approaches (or resources) to attack R&D challenges
- They target one or more 'neglected diseases'
- They use, or intend to use, variants of the multi-candidate/portfolio management approach
- Their primary objective is public health rather than a commercial goal
- They are focused on developing products suited for use in developing countries.

The other similarities among existing product development ventures stem from the nature of the product development process. While this is somewhat different for drugs and vaccines (and quite different for diagnostics), there are again major similarities. The progression involved in turning scientific knowledge into widely applied disease control interventions is shown in Figure 1 and can be termed the Research-Development-Access continuum.

[1] Widdus R. 2003. Public-private partnerships require thoughtful evaluation. *Bulletin of the World Health Organization*, 81(4):235.

[2] See annex 3a (Widdus R. *Background on PD PPPs under consideration at the workshop*).

Figure 1. Research-Development-Access continuum



This common continuum means that, to accomplish their mission, all product development PPPs need:

- the engagement of industry, public/governmental agencies and civil society organizations as necessary;
- sufficient resources to implement their chosen strategies;
- strategies for management of intellectual property and leveraging R&D investments to assure product access for the poorest populations;
- access to clinical trial capacity;
- access to regulatory experience including that relevant to low- and middle-income countries (LMICs);
- access to expertise in assessing need, demand and markets for their products particularly in LMICs;
- access to expertise in assessing production options and their costs;
- knowledge of the best strategies for delivering products to the poorest, including ways to work effectively with/within the existing health services infrastructure;
- ways of measuring progress, in product development or delivery, or health status; and
- strategies for ensuring that non-contractual allies, in their collective efforts to develop and improve access to health products, actually fulfil their responsibilities and obligations.

For success in development and application of products to combat neglected diseases, a range of complementary capacities must also be engaged (Figure 2).

Figure 2. Complementary capacities

These may need strengthening in parallel but not necessarily by the PD PPPs themselves.

For comparing ventures, others may find it useful for PD PPPs to adopt similar approaches. These include:

- Expressing their goals in a way that facilitates measuring progress and productivity
- Expressing their potential public health impact in a consistent fashion
- Projecting their financial needs, for funds both passing via the venture and through other channels, to accomplish their mission.

Underlying similarities between ventures may be obscured by the organizations' desire to portray themselves in particular ways or to emphasize slightly different philosophies. For example, some describe themselves as 'public-private partnerships', whereas others prefer to call themselves 'not-for-profit pharmaceutical companies' or 'virtual pharmaceutical companies', and yet others 'not-for-profit (R&D) initiatives'. Some seem comfortable being portrayed as collaborating closely with commercial pharmaceutical companies and actively seek such representation in their management processes (e.g. MMV), whereas others, such as DNDi, put more emphasis on the public sectors' responsibilities for ensuring product development for 'neglected diseases'.

Of necessity, all organizations tackling 'neglected diseases' collaborate with researchers and public health authorities in countries where these diseases are endemic. However, most do not regard capacity strengthening, separate from product testing, as a primary responsibility.

Variations among PD PPPs and their origins

One background paper prepared for the London meeting documents the variation among the PD PPPs under consideration along four themes:[1]

- Strategic variations
- Financial variations
- Sector roles and contributions
- Operational variations.

One way to understand this variation, and even perhaps predict it, is to examine the consequences of the mission chosen by those responsible for establishing the new venture. Specifically, the choice of disease and product focus determine to a significant extent a wide range of factors around which PPP operations vary.

The product/disease focus determines the nature of the scientific challenge (in terms of likely difficulty) as well as the scientific environment in which the venture starts to operate. Scientific research in some areas may have been more badly neglected over time than in others. This will make it more likely, and justifiable, that advocacy for the 'field' in general will be seen as a necessary task of a PD PPP, to ensure, for example, it has sufficient leads from basic research. This choice also affects the availability and range of commercial or other partners:

- A neglected field will generally have fewer potential collaborators either academic or commercial
- A partnership aiming to develop the first product in its class, or a new class of products (like microbicides), will have fewer potential commercial collaborators
- Those developing vaccines (compared to drugs) will find fewer collaborators interested in their activities and a very small number of major companies with vaccine development and large-scale manufacturing experience.

These situations contrast with that of groups where the field has been reasonably active and a variety of collaborators exist to repeat well established scientific tasks, as is the case for malaria drugs.

Partnerships with fewer potential overall collaborators are more likely to be active along the whole Research-Development-Access continuum (including advocacy) and to undertake more activities 'in-house'. These ventures are thus likely to need greater resources, principally because of the environment their mission bestows upon them.

The product/disease focus chosen also has significant implications for the potential uptake of products. For some combinations, more defined and/or better functioning purchase and delivery systems exist. For example, purchase and delivery of children's vaccines and drugs for tuberculosis is usually by (or for) governments. But this is not true for vaccines for adults

[1] See annex 9b (Sander A, Widdus R. *The emerging landscape of public-private partnerships for product development*).

and adolescents, such as will, at least initially, be the case for HIV/AIDS vaccines. Hence, IAVI identified the need to address access issues for its target products, as does IPM, which does not currently have an identifiable delivery system for its products.

Partnerships developing products for which purchase or delivery systems are less easily identifiable or function less efficiently face the quandary of how to ensure uptake of their products.

Thus variations around '**advocacy**' may reflect the perceived shortage of collaborators, while those around '**access**' activities may suggest the absence, or deficiencies, in downstream uptake systems.

Other variations, e.g., doing more work 'in-house', may reflect choices governed to some extent by the perceived absence of suitable partners.

Advocacy

In addition to activities strictly connected with product development, some PD PPPs elect to undertake various general communication and advocacy activities. The extent and nature of these, to a large extent, are governed by their perceptions of the status of the 'field' in which they operate and the position that they wish to occupy in it:

- All the ventures discussed here undertake communication and advocacy activities directed at mobilizing resources for their own mission.
- Some organizations (but not all) undertake to produce and disseminate information on issues and progress in their field of operations, aiming to both increase awareness and raise their own visibility. Examples include the IAVI Vaccine Bulletin.
- Some organizations undertake analysis and advocacy on issues that they feel are related to the likelihood that they will accomplish their mission. Examples include the work of IAVI and IPM, proposing that a range of regulatory issues be clarified and that regulatory processes be harmonized between countries.
- Advocacy on a slightly broader front is undertaken by some PD PPPs (such as the TB Alliance) for more investment in their overall field, especially if it has been neglected over a significant period of time. Similar motivations drive the advocacy activities of DNDi for those neglected diseases that are confined to the poorest population usually in tropical regions.

The choice of product/disease focus also has implications in some cases for the existence of potential 'advocacy allies' for pursuing the ventures' mission (beyond collaborators strictly for product development activities). Those engaged in HIV/AIDS can enlist grass-roots activist organizations in many industrialized countries, but which do not exist for diseases like malaria. Microbicide development groups can align with groups in both industrialized and developing countries which seek to empower women (to better control their health risks). Where health professionals associate nationally or internationally around particular diseases, these can also be useful allies for related PD PPPs.

Access

If no delivery system is identifiable, a PD PPP may see a need to outline an 'access' plan. While an access plan might be useful in all cases (to document assumption about policy or financing), it is most clearly needed in cases where no delivery system is immediately apparent. Where identifiable delivery systems exist but function poorly, it is also arguable that an access plan could facilitate actions, in parallel to actual product development, to strengthen delivery, so that more of the potential impact of a new product was eventually achieved. Suggesting that PD PPPs prepare a plan identifying steps necessary to achieve access does not imply that they would necessarily be the implementers. Others, such as government or international agencies, might be more appropriate and indeed have formal responsibility for the necessary actions.

Understanding typical PD PPP operations

While variations among PD PPPs make it difficult to generalize, some attempt is necessary so that readers new to the field have a general understanding of the way most of the PD PPPs considered here operate.

Candidate products need to be moved at the fastest possible speed and at reasonable cost through the various steps of product development. These have been described in most detail for drugs,[1] and are somewhat similar for vaccines, particularly at the clinical testing stages.

[1] Nwaka S, Ridley R. 2004. Virtual drug discovery and development for neglected diseases through public-private partnerships. *Nature Reviews Drug Discovery*, 2: 919—28.

Figure 1 (above) represents this chain generally for both drugs and vaccines. A more detailed picture for drugs has been published by Nwaka and Ridley.[1]

It is possible for a candidate product to enter the sphere of a PD PPP's influence at any point in the Research-Development-Access continuum, but often the venture negotiates the rights to develop further a candidate from an academic institution or company which typically hold patents on these.

To move any candidate product through the various product development stages requires certain types of testing and subsequent decisions on whether it has sufficient promise to try to move through the next stages. Failures, rather than successes, are the norm and it is most cost-efficient if decisions to abandon projects are made quickly and with the lowest expenditures.

To maximize the chances of success, it is best to have a number of candidate products at each different stage and to replace routinely those that are abandoned because the results of testing indicate problems, e.g. low efficacy, toxicity. This process of portfolio management has been refined for drugs (see Schmid[2]) but less studied for vaccines.

Each testing step in product development requires particular expertise and resources, such as laboratory equipment for synthesizing chemical variants of a candidate drug, animal models for toxicology testing or access to human populations at risk of the target disease or patients for testing candidate efficacy in preventing or treating it.

This expertise typically exists outside a PD PPP in other organizations individually (e.g., pharma companies) or can be brought together in project teams. PD PPPs draw upon these companies or assemble collaborative teams through contracts for the activities connected with moving candidates through specified testing steps. Based on the results of these activities, PD PPPs decide to pursue the candidate further or abandon it. Contracts are usually with organizations that share or support the PD PPPs' public health goals so the deals seek and often receive in-kind support (*see* Kettler and White 2003[3]). Deals frequently seek to combine contributions from different players that ultimately benefit both. This is illustrated in Figure 3.

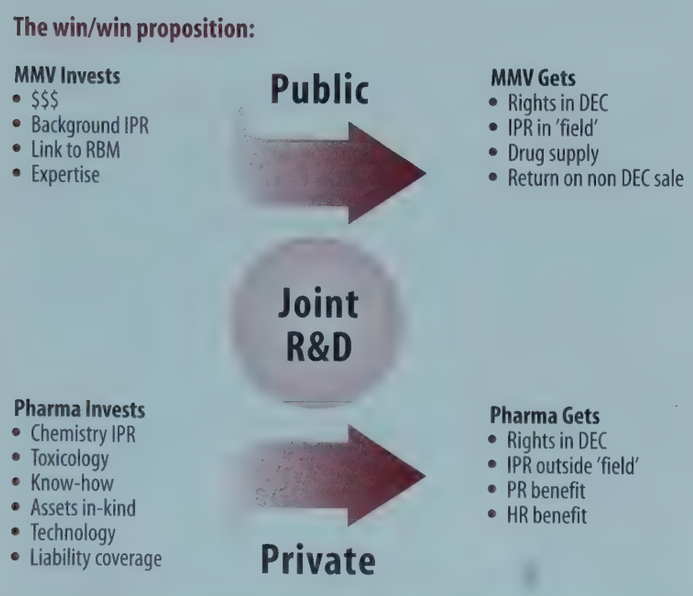
Sufficient expertise and staff need to reside in the PD PPP to manage the organizations or project teams contracted by it. If fewer potential collaborators can be found to take on the necessary work, a PD PPP will need to have a proportionally larger staff to manage or conduct activities 'in-house'. The length, complexity and expense of product development means that where there is a paucity of candidates and few collaborators, the funding needed by the PD PPP and the likely time to success will be greater.

The necessary expertise and composition of teams assembled to move candidate products through different stages in the research and development process vary with product type and development step.

Figure 4 gives an idea of the complexity of some arrangements.

As the vast majority of collaborators engaged in moving candidate products through testing steps are at a distance – physically and organizationally – from the PD PPP, the term '**virtual R&D**' has been coined to describe these arrangements, to contrast it with the process as historically practised in large pharmaceutical companies, where most employees and activities

Figure 3. Balance of incentives and costs: MMV and pharma partner

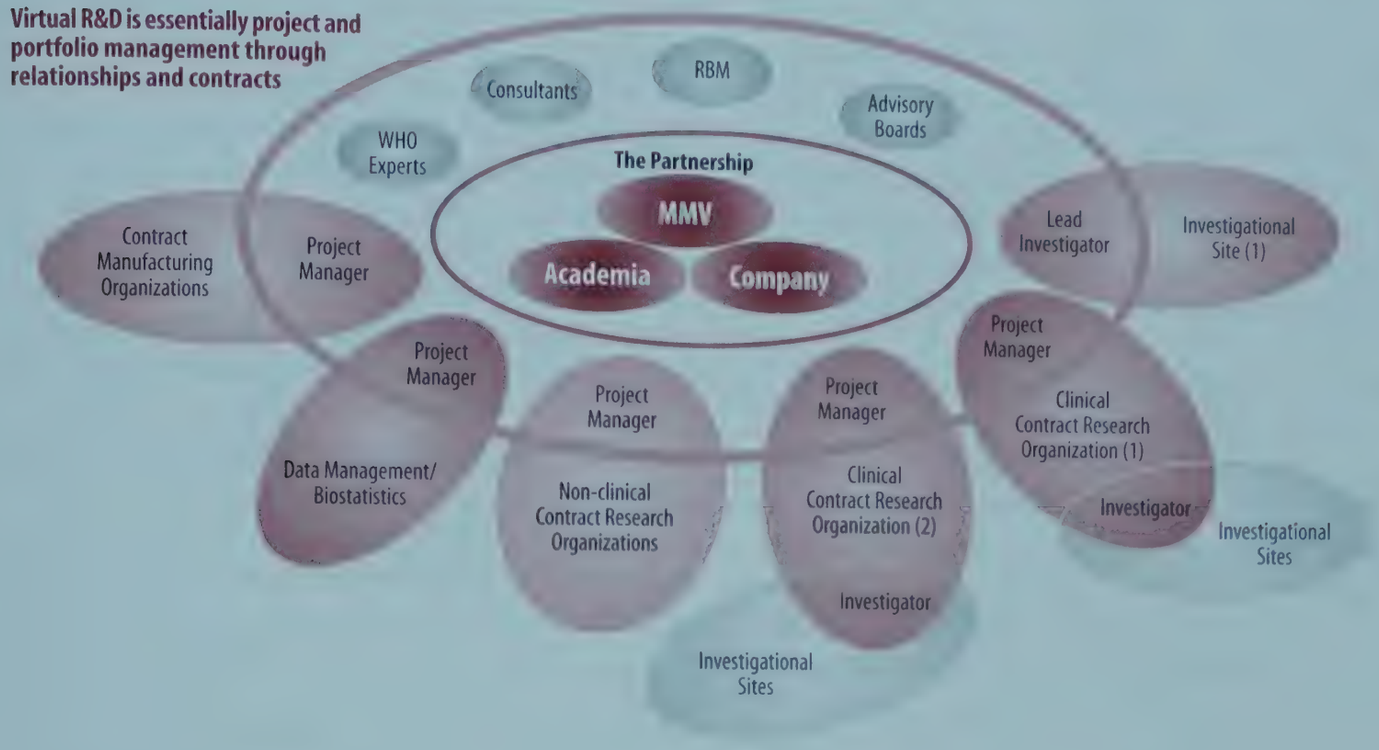


[1] Ibid.

[2] See annex 9d (Schmid E. *Portfolio management in the pharmaceutical industry*).

[3] Kettler H, White K. 2003. *Valuing Industry Contributions to Public-Private Partnerships for Health Product Development.* Initiative on Public-Private Partnerships for Health, Global Forum for Health Research, Geneva, Switzerland.

Figure 4. The complexity of virtual R&D management: An illustrative project of the Medicines for Malaria Venture



were 'in-house'.[1] In recent years, small 'biotech' companies have pioneered virtual operations as a way of conducting R&D with lower in-house investment in staff and equipment, thus maintaining their flexibility. Even large pharmaceutical companies are moving in this direction.

Some commentators have noted the extra management demands that virtual R&D places on its sponsors. However, there seems to be general agreement that it is a cost-effective alternative to the duplication by the PD PPPs or public sector organizations of existing (expensive) physical infrastructure for possibly short-term projects.

Most PD PPPs are not currently funding activities intended to translate ideas from basic research into candidate products (see Nwaka and Widdus[2]). Translational activities are hence reliant on major biomedical research funders, if they are undertaken at all.

The foregoing needs to be recognized as a general description of PD PPP operations. Selected illustrations of product development partnerships in operation, prepared by the named organizations, are included below. Readers interested in more detail are referred to the Sander and Widdus background paper,[3] plus the web sites and annual progress reports of the individual organizations.

Product development partnership in operation: Illustrations of the handling of typical challenges

From the operations of the existing PD PPPs, especially the older ones, a range of examples below have been selected to illustrate how they have met challenges frequently encountered in the development of health products.

Medicines for Malaria Venture (MMV)

Creation and management of a not-for-profit portfolio of candidate malaria drugs

■ MMV was challenged with the need to create and then actively manage a 'virtual R&D portfolio' from its founding in November 1999. At that point it had identified three drug discovery projects which met its product-specification criteria. It had also accepted, in

[1] Recently, pharma and biotech companies themselves have been adopting 'virtual R&D', for example, through contract research organizations.

[2] See annex 9f (Nwaka S, Widdus R. *The current research-to-development 'hand-off' process for product concept/candidate products and possible improvements in it*).

[3] Annex 9b (Sander A, Widdus R. *The emerging landscape of public-private partnerships for product development*).

its draft business plan (endorsed by its Board in March 2000), the idea that to succeed it needed to manage its portfolio in line with the pharma industry's 'best practice'. Today it manages a balanced portfolio of more than 20 projects ranging from discovery to phase III trials. It became clear soon after its foundation that there were important differences between PPPs and for-profit companies that would tend to alter such operational 'best practice'. Where these differences exist, they need to be clearly understood and factored in by PPPs.

Since it was using public and philanthropic resources to create its 'portfolio', MMV adopted an approach that was open and transparent to all interested parties. Roughly every two years, it issues a general call for project proposals. About 100 proposals are received, of which generally 10 to 20 are considered the most promising based on a range of predetermined criteria. These proposals are then further evaluated by MMV's staff and its Expert Scientific Advisory Committee (ESAC). The ESAC is composed of a range of internationally recognized malaria and drug development experts, including individuals from industry. For all, conflict of interest procedures are followed. Depending on the need to balance the portfolio, final selections are made for funding. Historically, between 5–10% of the initial number of proposals are added to the portfolio.

In for-profit companies, it is clear that that R&D investment is in the context of a general accountability to investors to maximize financial returns. In contrast PPPs have no way to 'value' their portfolios. The concept of a net-present-value related to future 'DALY's averted' does not exist in public health. Accountability is to a broad group of stakeholders and is generally expressed in terms of a future 'public health impact' – but present metrics for such future impact are vague. R&D goals are usually expressed with surrogates (e.g., MMV: one drug registered every five years) with a focus on sustainability rather than on high-value exits. In this respect the idea that PPPs are like venture capital funds (social venture capital was the concept that justified the V in MMV) is somewhat misleading.

Despite these differences the rationale for a portfolio management for MMV has easily been justified by three clear benefits. It has reduced risk by diversification of the project investments amongst several chemical classes and therapeutic targets. It has fostered internal synergies between projects that should allow the creation of added-value combinations of drugs that are both more effective and less likely to generate resistance. It has significantly reduced costs by sharing enabling technologies between projects, by the flexibility it gives to shift resources from less to better performing projects and, crucially, by the greater ease it gives management to terminate projects that are not meeting their milestones. Nothing saves more resources in pharmaceutical R&D that the ability to stop failing projects early. MMV has already stopped four projects.

Global Alliance for Tuberculosis Drug Development (TB Alliance)

A case study of PA-824 licensing

■ The Global Alliance for TB Drug Development (TB Alliance) designs its contractual arrangements to enrol the best scientific partners worldwide and to ensure that the resulting technologies are affordable, accessible and adopted by health-care workers and patients in countries with the greatest need. The TB Alliance uses ownership or rights to intellectual property (including assignment, inventorship, licensing, sublicensing and other appropriate legal mechanisms) to balance its interests with incentives that make the industrial development, production and commercialization of new drugs economically feasible.

In 2002, the TB Alliance signed a landmark agreement with Chiron Corporation to in-license PA-824 and its analogues. Recognizing PA-824's potential as a tuberculosis (TB) therapeutic, Chiron was keen to license its intellectual property to an organization committed to advancing its development for TB. The TB Alliance received worldwide exclusive rights to PA-824 and its analogues for the treatment of TB and Chiron pledged to make this technology royalty-free in endemic countries. Chiron retained the right to develop and commercialize the compounds for non-TB indications.

The TB Alliance immediately devised and is undertaking a cost-effective development plan for PA-824, which is overseen by a development team with support from the US National Institute of Allergy and Infectious Diseases. In its first two years of development, PA-824 has successfully passed major pre-clinical milestones and, if progress continues, could enter

clinical trials in 2005. The TB Alliance is also pursuing a backup programme initially evaluating two analogues of PA-824 that have demonstrated even greater potency in vitro than PA-824.

The PA-824 agreement demonstrates how the public-private partnership model can be leveraged to develop new products for the diseases of poverty and that the economic realities of drug development can coexist with a social mission.

International Partnership on Microbicides (IPM)

Royalty-free compound licence from Tibotec/Johnson & Johnson

■ Since women are biologically and socially more vulnerable to HIV infection than are men, preventive options that women can use are critically important components of global efforts to stem the HIV/AIDS epidemic. The mission of International Partnership for Microbicides (IPM) is to accelerate the development and delivery of microbicides, products that can be used topically to prevent HIV transmission, for women in resource-poor settings.

The ideal microbicide will kill or inactivate HIV before it can reach its target cell. A product that blocks HIV from attaching to or entering its target cell could be a second line of defence. Should the virus escape, a third approach is to inhibit HIV from replicating within cells, thus preventing it from spreading throughout the body.

Currently, there are several classes of HIV therapeutics that are being successfully used to treat HIV-infected patients, and pharmaceutical companies are actively pursuing development of new generations of these compounds. Many of these drugs could be formulated for topical delivery to prevent HIV infection. To address this need, IPM entered into an agreement with Tibotec Pharmaceuticals Ltd, a subsidiary of Johnson & Johnson, to develop the promising compound TMC120 as a microbicide. TMC120 belongs to the class of drugs known as NNRTIs (non-nucleoside reverse transcriptase inhibitors), which are already widely used therapeutically to treat people living with HIV/AIDS. This agreement marked the first collaboration in the microbicide field between a major healthcare company and a public-private partnership such as IPM.

Tibotec developed TMC120 as an oral AIDS drug in the early 1990s, but has since adapted it into a gel that is currently in phase I clinical trials. Under the arrangement, Tibotec provides a royalty-free licence to IPM to develop, manufacture and distribute TMC120 as a microbicide in resource-poor countries. Additionally, IPM will look to develop other formulations with TMC120, both alone and in combination with other active ingredients. Under the agreement, Tibotec will bear the cost of the compound through phase II testing and will remain active as a scientific advisor.

Agreements such as this benefit both organizations. Through these arrangements, IPM and other non-profit microbicide developers can significantly expand the pipeline of promising candidates for development. Pharmaceutical companies can minimize the risks (proof-of-concept; regulatory; market size) of developing a new class of products by transferring the development of the drug to another entity. Should the product be licensed, both IPM and Tibotec will have achieved their goals.

International AIDS Vaccine Initiative (IAVI)

Underpinning AIDS vaccine development through laboratory networking

■ The current tests used to measure the immunogenicity of HIV vaccines are relatively new and can be highly variable in terms of protocols and reproducibility. Standardization across multiple clinical trial sites and products is, therefore, a challenge not only to IAVI but the field. The IAVI Core Laboratory was established so that valid head-to-head comparison of multiple candidate HIV vaccines could be made.

The IAVI Core Laboratory, based at Imperial College, London, UK, performs immunogenicity evaluations of IAVI-sponsored AIDS vaccine candidates. Volunteers who participate in trials have blood taken to assess whether a vaccine induces a measurable immune response. IAVI currently sponsors clinical trials of four different HIV vaccines, which are under way at 15 trial sites in Uganda, Kenya, South Africa, the UK, Belgium, Germany, Switzerland and the US, in addition to sites in Rwanda and India which are poised to commence their first HIV vaccine trials. In each of these trials, volunteers' blood must be processed so that immunogenicity assays can be performed. An absolute requirement of operating vaccine trials at multiple sites

is that a valid comparison be made between performance of different vaccines both within and across trials. Furthermore, this data must be collected under conditions in accordance with internationally recognized standards. These issues are especially important in the search for an AIDS vaccine, in light of the overwhelming public health consequences of achieving shortened vaccine development timelines – a major goal of IAVI.

In order to facilitate valid comparisons, the IAVI Core Laboratory receives samples from all clinical trial sites to test. The tests at the core laboratory have been validated according to international standards and the laboratory environment is also accredited. In addition the laboratory is the focal point in the effort to standardize procedures across all sites engaged in separating blood and testing samples from trial volunteers. Activities that are key to standardization include providing validated Standard Operating Procedures (SOPs), standard reagents, standard validated equipment, on-site and field site training and support of trial site staff, in addition to acting as a primary field laboratory for IAVI-sponsored trials under way in London. Furthermore, IAVI holds workshops in which trial laboratory staff are invited to learn and henceforth apply the principles in line with regulatory authority guidance for data submission in support of vaccines.

The net outcome of using one laboratory to coordinate the entire IAVI programme, through provision of identical operating procedures, reagents and training, ensures the data are reproducible across sites in identifying positive responses. Thus IAVI benefits from this through being an accredited lab, hence assuring the quality of the data. Trial sites benefit from this set-up through reducing the lead-time required for involvement, and also the one-stop direct assistance provided by the core lab. Both the sites and core lab team benefit from being brought together in the wider training efforts, which aid staff and hence site development, and also from the sense of partnership, unity and combined purpose in the greater effort of developing an AIDS vaccine.

The vaccine network field benefits through the transparent and collaborative work that the core lab participates in. This occurs with other groups in the HIV vaccine network and outside, such as the TB Initiative, both through exchange of SOPs, and within the HIV vaccine network participation in proficiency tests. These collaborations help move us closer to being able to compare data across networks, which will benefit the field in driving towards the goal of an HIV vaccine.

Aeras Global Tuberculosis Vaccine Foundation

Preparing for large-scale clinical efficacy trials

■ Recognizing that testing of new vaccines for efficacy against tuberculosis would represent a significant logistical challenge and potential bottleneck, the predecessor to the Aeras Global TB Vaccine Foundation (then named the Sequella Global Tuberculosis Foundation) initiated a programme to anticipate this need.

South Africa was chosen for the development of a clinical site and of human resource capacities, because of the prevalence of TB and the level of existing capacity there. At the time of early discussions, the South African Government had made the decision to switch from percutaneous administration of a locally manufactured strain of the Bacillus Callmette-Géurin vaccine (BCG Tokyo) to the intradermal administration of Danish-manufactured BCG strain 1331. This offered the opportunity for development of clinical trials capacity in the Boland-Overberg region of Western Cape Province (east of Cape Town) through the conduct of a randomized, controlled trial of an existing TB vaccine, at the same time answering immediate scientific questions.

Enrolment began in March 2001 and was completed in July 2004 with the enrolment of 11,677 neonates within 24 hours of birth. In addition, blood was collected at 10–14 weeks of age from 5,467 infants and Peripheral Blood Mononuclear Cells (PBMCs) banked in liquid nitrogen to allow for future nested case-control studies comparing the immune response among those who develop TB with those infants who are exposed in the household and do not develop the disease. Follow-up will continue through July 2006.

The overall Clinical Site Development Programme in South Africa was designed to characterize the TB problem among neonates in the collaborating communities in the Western Cape region and to prepare for Phase III trials of new vaccine candidates. Among the lessons learned are that the surveillance may be impacting on the measurement of the incidence of tuberculosis. Over 200 cases of culture and Acid Fast Bacilli (AFB) smear-positive tuberculosis have already

been identified in this cohort with a 2.3% incidence estimated during the first two years of life by a life-table technique. However, many of these cases are asymptomatic and have normal chest X-rays. All received a full course of four-drug chemotherapy so it is unknown whether these infants would have gone on to develop symptomatic TB disease or if the infection would have resolved on its own. Since TB occurrence of tuberculosis disease is likely to be the primary endpoint in a phase III study, it is important to resolve the natural history of disease in infants and therefore additional studies are planned. Aeras also plans to conduct a large cohort study among adolescents (12–18 years old) in the same community to prepare for phase II TB vaccine trials in this age group.

In addition, Aeras has collaborated with South African colleagues to develop a Professional Development Programme that provides required background on clinical research and a foundation for later training in protocol procedures. The programme is designed to meet the needs of adult learners and to be accessible to the entire range of staff, including those who left school short of high-school graduation and those who may have bachelor or other college degrees.

Aeras has also undertaken a similar capacity development effort in India, working with colleagues in the Institute of Population Health and Clinical Research at St. John's Medical College in Bangalore, India, to develop a site in Palamaner District in Andhra Pradesh. Activities here will be partially funded by a recent US$ 3 million award from CDC in the US. Neonatal and adolescent cohort studies as similar as possible to those Aeras is sponsoring in South Africa will be conducted, and the Professional Development Programme will also be implemented at this site.

Institute for OneWorld Health (IOWH)

Moving from clinical trial to regulatory approval in disease-endemic countries

■ To protect the health of citizens in disease-endemic countries (DECs) where infectious diseases are rampant, it is critical to move a compound through clinical trials and the regulatory approval process as quickly as possible. The challenges in doing so are many and involve demonstrating clinical effectiveness and safety under conditions which are frequently less than desirable; finding a manufacturer, which can produce the drug that is affordable by the patient; getting the drug approved by regulatory authorities as soon as possible; and getting it distributed to a patient population, part of which may be located in isolated rural areas.

At the Institute for OneWorld Health, we are currently developing an off-patent aminoglycoside antibiotic that is no longer marketed, paromomycin, for the treatment of visceral leishmaniasis. This drug is initially intended for India and subsequently for other DECs. Its development is very important to us, not only because it can save hundreds of thousands of lives, but because it will show that our business model of combining foundation and charitable donations within a pharmaceutical company model, partnering with companies and organizations in the developing world, yields an effective pathway for developing pharmaceuticals for the treatment of infectious/parasitic diseases in the developing world.

To meet the challenges we face, we are partnering with charitable foundations, international health organizations, pharmaceutical companies and NGOs. Our staff is composed of scientists and clinicians who have had many years' experience in drug development in the international biopharmaceutical industry, as well as chemical and manufacturing consultants, and regulatory affairs consultants with international experience.

Our phase III paromomycin efficacy clinical trial, being conducted in India, is funded largely by the Bill & Melinda Gates Foundation. Our partner, WHO/TDR, is providing clinical monitoring. Paromomycin will be manufactured at a cost patients can afford by the International Dispensary Association of the Netherlands and its subcontractor, Gland Pharma, of India according to the US Food and Drug Administration (FDA) good manufacturing practice (GMP) standards. Regulatory filings will be made in targeted DECs, initially India. To enhance regulatory approval, we will work closely with target DECs' regulatory authorities, and are considering seeking orphan drug status and fast-track approval by both the European Medicines Agency (EMEA) and the FDA, because DECs frequently approve drugs undergoing regulatory approval by these agencies more quickly. Lastly, we will work with NGOs to establish distribution mechanisms for getting the drug to patients, as well as monitoring its clinical use and effectiveness.

The success of this project will demonstrate how

partnering enhances the effects of participating organizations to bring a drug to DEC patients more quickly, potentially saving hundreds of thousands of additional lives.

International AIDS Vaccine Initiative (IAVI)

Ensuring rapid access to preventive HIV vaccines

■ AIDS is the greatest public health challenge of our time. Over 40 million people have HIV or AIDS and over 14,000 people are infected each day. Prevention programmes are helping to slow the spread of HIV, but there is an urgent need for improved and easier-to-use prevention technologies. Vaccines are among the most cost-effective public health technologies available, and a safe and effective HIV vaccine would make a significant difference to current efforts to control the epidemic.

Once a vaccine is developed formidable barriers still stand in the way of rapid global access. Historically, developing countries have waited an average of 15 years or more after new vaccines have been licensed in industrialized countries before getting them themselves. This is clearly unacceptable – but to change it will take proactive and coordinated action from governments, the private sector, international agencies and community organizations throughout the world. And this action needs to start now. With prompt action the world could use a preventive vaccine to avoid the inequities we now witness in HIV/AIDS treatments. Waiting to address access issues until after an HIV vaccine is licensed will be sentencing millions to preventable illness and death.

IAVI was established with the twin objectives of speeding the development of an HIV vaccine and of ensuring that when a safe and effective vaccine is developed it is widely used in developing countries. A crucial component of IAVI's work lies in supporting the development and implementation of policies to ensure rapid access to HIV vaccines. In partnership with other stakeholders, IAVI is working to ensure that the necessary policies, mechanisms and infrastructure will be put in place well in advance of a vaccine being licensed.

Among the challenges that IAVI believes need to be addressed are:

1. Developing sustainable global financing and vaccine pricing mechanisms to ensure that vaccines are widely available.
2. Minimizing delays in access by ensuring that there is ample manufacturing capacity available to meet global demand at the time a vaccine is licensed.
3. Investing in the development and/or strengthening of appropriate delivery systems, policies and procedures for reaching adolescents, sexually active adults and other at-risk populations.
4. Ensuring that there is ample clinical trial and regulatory infrastructure to fast-track HIV vaccine clinical trials and to streamline and coordinate the licensing of an HIV vaccine.
5. Supporting the development of regulatory skills in developing countries so that they have the capacity to review and approve HIV vaccines in a timely fashion for use in their own populations.

Product development partnerships: Still an evolving field

The foregoing outlines the early history of the not-for-profit product development ventures that have recently emerged and illustrates their operations.

For the reasons outlined in the Preface, IPPPH and the meeting co-organizers, the Bill & Melinda Gates Foundation; the Department for International Development, UK; the Rockefeller Foundation; and the Wellcome Trust concluded that a critical review would be warranted and hence convened the meeting on 15–16 April 2004.

The meeting showed that the field is dynamic. Every few months another interesting example is added to the illustrations above about how product development partnerships go about their respective missions.

The London meeting and this report of the state of the field of product development partnerships will undoubtedly need revisiting periodically. The following summaries represent a first – and probably imperfect – attempt to survey an evolving field.

Meeting summary

Katherine White

Background

A workshop "Combating diseases associated with poverty: Financing Strategies for Product Development and the Potential Role of Public-Private Partnerships"[1] was organized by the Initiative on Public Private Partnerships for Health (IPPPH)[2] in collaboration with the Rockefeller Foundation, the Bill & Melinda Gates Foundation, the UK Department for International Development and the Wellcome Trust. Prior to the workshop, IPPPH commissioned a comprehensive set of background papers to help prepare participants (see annex 9). In both the background materials and meeting discussions, attempts were made to elucidate the significance of the many differences among product development public-private partnerships (PD PPPs) for their funding requirements and probabilities of success.

Participants at the meeting represented a broad array of current and potential actors in the field from the PD PPPs, their funders, the private sector and other constituents.[3]

The workshop was organized around the following five objectives:

- Provide background on the emergence and operations of the PD PPPs.
- Consider how PD PPPs and other players operate and interact.
- Assess the current and future financial needs of PD PPPs.
- Assess if innovative financing options for diseases of the poor exist.
- Identify questions and issues requiring further attention and study.

Meeting discussion themes

During the two days of discussion it became clear that as a group, PD PPPs could be thought of as a coherent field, albeit with broad differences driven by the environment in which they operate. As product developers for 'neglected diseases', or diseases of poverty, the PD PPPs share underlying similarities, as well as differing on many features and the context in which they operate.

Discussions during the meeting covered a number of areas surrounding the current understanding of the PD PPP field and its future needs. The main themes of this discussion are summarized in the following sections:

- PD PPP model
- Key interfaces with other organizations
- Role of portfolio management
- Preparing for access: availability and adoption
- Financing
- Judging success
- Role of coordination

PD PPP model[4]

There was general agreement that the PD PPPs are a coherent group and that the model is a sound approach to bridge the gap that has existed between basic research and the need for new products to control/combat diseases of poverty. Their activities are generally characterized by:

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[1] Held at the headquarters of the Wellcome Trust, London, UK, 15–16 April 2004.

[2] A component of the Global Forum for Health Research, established to monitor, analyse and support ventures in public-private collaboration to reduce global health inequities associated with poverty.

[3] For full list of participants see annex 2.

[4] See annexes 9b (Sander A, Widdus R. *The emerging landscape of public-private partnerships for product development*) and 9l (Ridley R. *PD PPPs for diseases of poverty. Are there more efficient alternatives? Are there limitations?*).

- A focus on product development for diseases of poverty.
- Use of private sector management practices including portfolio management and industrial project management.
- Advocacy for their own work and often for global attention to their disease(s) of interest.

However, there was also recognition of the differences in approach across PD PPPs as a result of:

- Technical differences in drug, vaccine, microbicide and diagnostics/device development.
- The extent to which individual PD PPPs have implemented portfolio management.
- The specific context in which an individual PD PPP is operating, including scientific development and political will associated with the disease(s) of focus.

One challenge is to communicate the core strengths and perceived benefits of the model with simple messages that cut across the entire field of PD PPPs to encourage a broader support base (see also subsection on financing, below).

PD PPPs are not an end in themselves but are a practical way to help address a specific public health inequity that characterized the 1990s: the near-total lack of development of essential new products for the diseases of the poor. In particular the use by PD PPPs of portfolio management is a key distinguishing feature of this new field, very different from the linear approach to vaccine and reproductive technology development that has sometimes been pursued by the public sector in the past. On their own PD PPPs are necessary but not sufficient to address the global health needs outlined in the Millennium Development Goals.[1]

Each pursues its own strategy, driven by the economic and social context in which they are operating to ensure development and access to its products. This affects every decision point along the product development pipeline from acquisition of candidate products, to the choice of manufactures, to the need for strong partnerships with donation programmes, procurement programmes and/or other 'pull' mechanisms to ensure the neediest and poorest populations around the globe benefit from the products that result from the PD PPPs efforts.

Open questions

- Should the PD PPP field continue to proliferate or have the most important opportunities already been addressed?
- How should funders balance their investments in PD PPPs with other approaches to product development (e.g., funding the private sector directly, or funding individual projects)?
- How should funders balance investments in access to existing products with investments in new product development?
- What is the right balance of public and private sector goals, staff and managerial approaches for the PD PPPs? How will this vary as the PD PPPs mature?

Key interfaces with other organizations

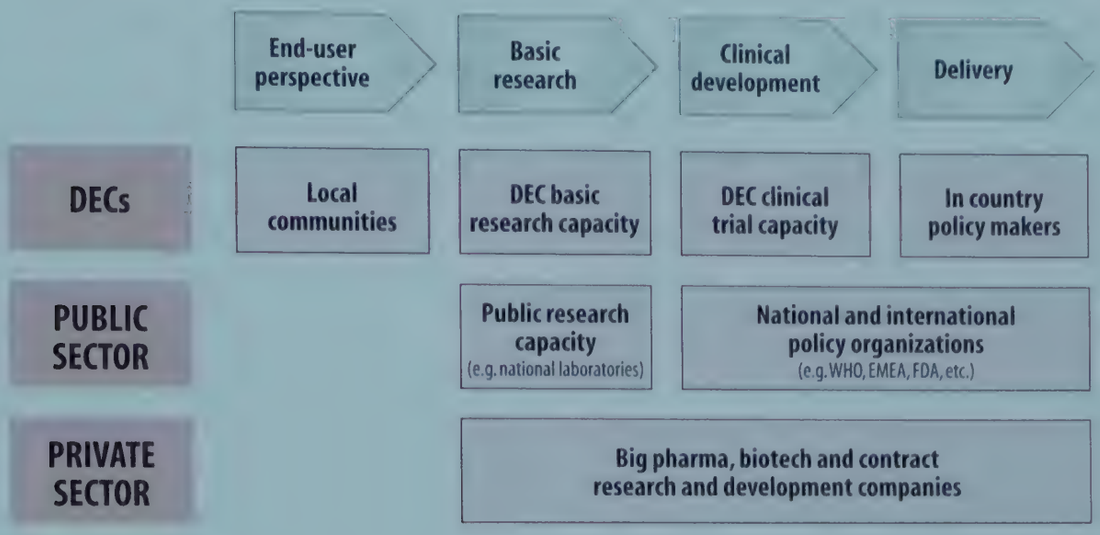
Within the commercial world of product development, effective management of interfaces with other companies and institutions is critical for success. Due to the cross-functional nature of the development process there is an increasing emphasis on the complex outsourcing networks throughout the R&D continuum. The private sector also benefits from the focus and essential discipline instilled by a commercial market, in which success is easily quantified by the bottom line.

Traditionally for big pharmaceutical companies, many of the connections that need to be made are internal. In pre-clinical development, for example, in-house chemists, biologists and toxicologists must work together to determine a target molecule's suitability for progression to clinical trials. This is not the case for PD PPPs.

Most PD PPPs, like many biotech firms, are relatively small and achieve a large portion of their work through others, by connecting the requisite people, communities, organizations and companies to achieve their goals. Depending on the state of the science and the nature of the products and disease targets, the focus of activities along the spectrum from research to development to access may vary. Whatever role a PD PPP itself takes on, effective management of interfaces with, and "hand-offs" to, others remains central to its

[1] See annex 5 (United Nations Millennium Declaration, *United Nations Resolution 55/2 2000*).

Potential interfaces for PD PPPs along the development chain



strategy. Since product development is at the core of all PD PPPs, interfaces with the following players were recognized as important to all PD PPPs:

- Disease-endemic countries (DECs)
- Public sector
- Private sector

Disease-endemic countries

Disease-endemic countries already provide valuable contributions to product development all the way from research to end product delivery and use. Increasing DEC involvement will help build ownership of potential products and increase the potential for successful delivery and adoption of new products.

As discussed above, there may be further opportunities to link directly investment in basic research and system strengthening in these countries with the work of the PD PPPs. The DECs are also integral to three other components of the development process, providing the end-user perspective, clinical trial capacity and in preparation for access.

End-user perspective

Developing drugs and other products that will be used and embraced by those in need requires early consideration of their needs and perspectives. Within both big pharmaceutical and biotech companies, the involvement of their commercialization groups (those with the greatest customer insight) begins early in the process as the candidates' transition into pre-clinical and clinical development. It is just as important for PD PPPs to get the same kind of market input; a product has no value if it is not used. Many of the PD PPPs are already getting some involvement through their boards, scientific advisory bodies and through sophisticated market analyses. It was very clear that involvement of the ultimate customers and generating ownership at the country level is integral to success and is not an optional extra.

Basic research

There was a strong feeling during the discussions that in the longer term research from DECs could play an important role in contributing to the overall success of the PD PPPs. In the shorter term, one idea to increase the flow of leads that was discussed was strengthening the links between PD PPPs and existing research communities in disease-endemic countries. Another area of discussion included the potential for traditional medicines, widely used throughout Africa, China and South-East Asia, to provide an additional source of potential candidates.

Today, while there may be applicable research, these communities often do not have strong technology transfer skills. It may be beneficial to go further than creating direct links to PD PPPs by setting up centres of excellence around specific disease areas in some countries. Centres of excellence could help provide the criti-

cal mass and focus characteristic of successful research groups in the commercial drug world and would provide a natural interface point for linking into specific PD PPPs. It could also have the added benefit of bringing the local 'customer' (or intended beneficiary) perspective into the development process earlier and building research capabilities in these countries. It was generally agreed that PD PPPs should not be expected, as a principal goal, to address the need for research strengthening in disease-endemic countries.

Clinical trial and regulatory capacity

Effective clinical trials require physical sites, ethical review capacity and the appropriate regulatory bodies to support the trial and ultimately approve the product for use. In sub-Saharan Africa, where many of the products will need to be tested, there is a shortage of all three. Bridging this gap will require scientific and regulatory leadership as well as significant investment in funding.

- *Trial sites:* With more than 300[1] products for 'neglected diseases' in development globally there is not the trial capacity to support the current pipeline. In response many groups are independently investing in trial site capacity (e.g., individual PD PPPs and the European and Developing Countries Clinical Trials Partnership [EDCTP]). Given the high cost of such investment there may be benefits from increased coordination in this area where possible. Once established it will also be necessary to ensure a steady flow of projects to sustain them. (See also IPPPH 2004.[2])
- *Regulatory capacity:* In many of the countries where trials could be conducted, there is limited local regulatory capacity to provide approval for such trials and successful products. While trials can be run under the guidelines from other recognized regulatory bodies (e.g., the United States' Food and Drug Administration [FDA]) the absence of such capacity is one of the reasons many industry players choose not to run trials in these countries.
- *Ethical review capabilities:* Credible research cannot be conducted anywhere without two review capabilities: the ability to gain informed consent; and the presence of effective ethical review committees. While committees are being established they are often of poor quality due to the limited training and awareness of international standards.[3] In cases where researchers work with an international Institutional Review Board (IRB), the board may not be as sensitive to the issues raised by the local culture[4] (e.g., the need for consultations with families and communities). Local researchers need to be trained so that they can play a role in determining the nature and type of ethical guidelines used in international collaborative research.

For sub-Saharan Africa, one of the options discussed was to develop capacity in a representative set of African countries; balancing the potential benefits of focus with the benefits that capacity building in a broader set of countries could bring. However, increased DEC involvement in product development cannot be the lone burden of the PD PPPs (e.g., capacity building for research, regulatory infrastructure, etc.). While it is clear that PD PPPs will need to work closely with developing countries in this area, leaving the task to the PD PPPs would risk losing the focus that they bring to the product development. A challenge for the PD PPPs is how to leverage their collective voice to facilitate increased focus and momentum from organizations such as WHO, which can help by working in parallel with them.

In the future it might be possible to see some PD PPPs basing themselves in DECs. However, this is unlikely while R&D and innovation primarily occurs in developed countries.

Delivery

Disease-endemic countries will also play a critical role in working with the PD PPPs to ensure access and delivery of the products that are developed. See subsection Preparing for access: availability and adoption, below.

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[1] See annex 9h (Kimanani E, Clements V. *Current status of clinical trials in Africa*).

[2] IPPPH. 2004. *Clinical Trial Capacity in Low Income Countries: Experiences, lessons and priorities for strengthening.*

[3] See annex 9g (Leke R. *Ethical review capacity: Country needs, role and responsibility of partners and researchers*).

[4] "83 per cent of the developing-country researchers surveyed criticised US IRBs for being insensitive to local culture" Ethical review of health research: a perspective from developing country researchers, Hyder et al. *J Med Ethics.* 2004.

Public sector

Basic research

PD PPPs have three primary sources of product concepts for drug development:

- Development or modification of an established product for new indication(s).
- Continued development of previously abandoned products (often abandoned due to lack of commercial market).
- Development of totally new products.

Development of totally new drugs requires novel product concepts or leads from the basic research community (e.g., academic laboratories) to be fed into the product pipeline. 'Translation' is the term used to describe this transfer from basic research into product development. Ensuring that a flow of high-quality ideas are translated into products requires clear communication of the target product you are trying to develop, as well as awareness in the research world of how to channel ideas into PD PPPs or other development mechanisms.

In recent years there has been a significant increase in the flow of leads from basic research into commercial drug development. Universities and other research institutes are paying more attention to the benefits they can reap from successful translation of their research with many employing technology transfer managers. While there is often funding of basic research for most of the neglected diseases being targeted, there is still a struggle to translate this investment into potential medicines. From the discussions during the meeting translation efforts today appear to be facing two main challenges: scarcity of practical product-directed research; and the mechanisms to flow potential leads into PD PPPs.

For most academics working in research there is little incentive to focus on practical product-directed research when credits and accolades are more prevalent for basic research. Given that academics are primarily judged on the number of publications they produce and how much grant money they bring in, funding organizations could play an important role in changing some of the incentives. They could help make it attractive for PhD students and academics to push research until product developers can adopt it. For most of those funding basic research today this would require an increase in understanding about the importance of translation and the process.

Even where there is a high level of awareness of the benefits of technology transfer and there are potential leads or candidates that could be applied to neglected diseases, many of the technology transfer managers are not aware of the public health impact they could be having. There may be opportunities for them proactively to include intellectual property clauses in their agreements to ensure potential applications for neglected disease are not lost. For example, Yale University recently licensed a compound for commercial development for athlete's foot and reserved the rights for any indications in support of Chagas disease. Technology transfer in universities is largely driven by metrics, such as numbers of patents licensed and income to the universities, raising the question of how to encourage consideration of public health issues as well as raising awareness of the routes into global health.

Even if promising leads are generated and identified there is the challenge of translation itself. In many cases the skills and resources needed to help ensure successful translation reside largely within the private sector (e.g., development of assays, compound libraries, production scale-up, development of analogues, medicinal chemistry, etc.). Many PD PPPs are already working with subcontractors or negotiating in-kind contributions from the pharmaceutical industry to help enable the flow of novel product-focused leads into the pipeline, but more attention in this area is still required.[1] There was strong feeling during the workshop that any investment and capacity building to improve translational capabilities should pay equal attention to opportunities in both the developing and the developed countries.

For the future of the field it is imperative to increase awareness and the level of investment in product-focused research and translation mechanisms. Without a steady flow and successful translation of potential leads. the PD PPP model will not be sustainable.

Clinical development, regulatory approval and delivery

Much of the work the PD PPPs do to develop and manufacture new products requires either approval

[1] See annex 9f (Nwaka S, Widdus R. *The current research-to-development 'Hand-off' process for product concept/candidate products and possible improvements in it*).

from existing regulatory authorities (e.g., FDA and the European Medicines Agency [EMEA]) or, where available, from country regulatory bodies. As discussed above, in many of the countries for which the products under development are intended, there is not sufficient regulatory capacity. As a result PD PPPs must work within existing regulatory frameworks which often have a very different risk benefit threshold. In other cases, such as microbicides, the existing regulatory bodies do not have the necessary experience in approval and registration of the class of products. During discussions at the workshop there was strong feeling that coordination amongst PD PPPs and those organizations supporting them could help increase pressure on existing bodies to address the desperate need for regulatory harmonization and simplification.

As the PD PPPs plan for the success of their development efforts, they must also work in parallel with other organizations and groups to ensure that public policy, financing and infrastructure are ready once a product has been successfully developed.[1] Many of the gaps in resources or capacity highlighted during the workshop's discussions could be addressed through existing public sector organizations (e.g., WHO, UN and bilateral organizations). In particular some of the capacity building (e.g., translational capabilities, regulatory capacity, delivery infrastructure, etc.) and systemic issues (e.g., rapid public policy formulations, regulatory harmonization, etc.) are already within the remit of these organizations. The issue appears not to be one requiring new organizations but an increase in focus and attention on the issues. (See also subsection Preparing for access: availability and adoption, below.)

Private sector

Many of the skills required by the PD PPPs – both now and, increasingly, in the future – lie within the private sector. While many PD PPPs have links to private industry there was strong agreement that increased private sector involvement would be beneficial. The private sector today has been a source of both candidate products and access to technical expertise and physical resources, areas that will continue to be important in the future. Examples include:

- *New research technologies:* While the exact benefits are not yet clear technologies such as genomics or platform technologies should offer opportunities to improve the quality and flow of leads.
- *Manufacturing:* Formulation, scale-up, quality control.
- *Regulatory:* Management of the process of submission and reviews.
- *Market assessments:* Market sizing and economics.
- *Post-launch activities:* Pharmaco-vigilance, product liability.
- *Intellectual property.*

A better understanding of the current barriers to private sector participation is required if the level of involvement is to be increased significantly. Historically one of the greatest barriers to greater involvement, in addition to the opportunity cost, has been reputational risk given the political nature of the diseases and settings involved. Among some of the workshop participants, there was a strong belief that such an increase will only come from top-down support, driven by chief executive officers or senior research officers.

While big pharmaceutical companies have many of the significant expertise and physical resources required, the biotech community also offers a valuable source of resources. The biotechs may not have all the resources of big pharma available but they are likely to have different opportunity costs than their larger counterparts. The private sector could have several motivations for getting further involved with PD PPPs, starting from a humanitarian desire to do the right thing, opportunities for good public 'image' and the benefits that come from people in the company feeling good about what they are doing. However, their involvement needs a good business case, as private companies must ultimately satisfy their investors. One of the challenges for PD PPPs is to encourage the private sector to articulate what it will take to get them involved and to explore innovative ways to work together.

One promising area of opportunity is innovative licensing agreements with the private sector. This is especially the case in instances where a private drug company has already started the development of a particular product for which there may be both a commercial and a public health market, but where the

[1] See annex 9i (Ghosh G. *Emerging lessons in preparing for uptake of new vaccines*).

development risks outweigh the potential commercial benefits to the company. PD PPPs are already benefiting from licensing high-potential products in such a way as to ensure technical support in conjunction with the product while reserving the benefits from potential commercial applications for the private company. The recent deal between the International Partnership for Microbicides and Tibotec (affiliated with the Johnson & Johnson companies),[1] is just one example of the types of deals PD PPPs for both infectious diseases and contraceptives have been able to reach.[2]

The biggest opportunity, however, is to build markets where companies can expect a reasonable return from their investment (e.g., through pull mechanisms and/or tiered pricing structures).

Open questions

- What is the right balance for PD PPPs between getting the product development done and ensuring upstream and downstream gaps are filled?
- What will help ensure that links between the PD PPPs and different sources of research in their field are strengthened? What are the best opportunities to strengthen links with research in disease-endemic countries?
- How could the development of research centres of excellence aligned with specific diseases be encouraged?
- Could incentives for facilitating action be put in place to make it attractive for PhD students and academics to push research to the point where it could be adopted by product developers?
- Can more be done to increase awareness among technology transfer offices of potential routes into meeting global health, as well as commercial, opportunities?
- How can issues of clinical trial, regulatory and ethical review capacity be handled to address the needs of the PD PPP field?
- What will it take to capture the attention of senior management within the private sector and thus increase their involvement with and support of PD PPPs?
- How best to increase speed and focus of public sector organizations on critical path investments that will facilitate successful development and introduction of drugs, devices and vaccines? Can PD PPPs articulate their needs and priorities collectively?

Role of portfolio management

Many meeting participants familiar with product development repeatedly emphasized the length and the riskiness of the process, with attrition of candidate products expected at every stage along the research-development-access (R–D–A) continuum.[3] Portfolio management evolved in the private sector as a vital process by which to limit risk, manage the flow of products to market and minimize the cost of the drug development process.[4] Portfolio management has two key components:

- Diversification to reduce the reliance on a small number of candidates with similar characteristics and to ensure that the flow of products through the pipeline is smooth (i.e. enough products at different stages of development).
- Rigorous processes to ensure candidates that do not meet the specifications are weeded out.

Since most product candidates will fail somewhere along the development pipeline, management of multiple candidates helps to insulate funders from the risks inherent in health product development. The success of portfolio management is also highly dependant on the quality of the leads fed into the pipeline, reinforcing the importance of effective translation from research to development for PD PPPs. The availability of the right human resources and skills to ensure the process is run effectively is just as important for the PD PPPs as it is for the private sector.

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[1] Under the arrangement, Tibotec provides a royalty-free licence to IPM to develop, manufacture and distribute TMC120 as a microbicide in resource-poor countries. Tibotec has already developed a TMC120-containing gel, which is currently in phase I clinical testing. IPM will assume responsibility for development of this compound. Under the agreement, Tibotec will bear the cost of the compound through phase II testing and will remain active as a scientific advisor. *IPM Press Release*, 29 March 2004.

[2] See Kettler H, White K. 2003. *Valuing Industry Contributions to Public-Private Partnerships for Health Product Development*, IPPPH, and other examples in the full version of this report.

[3] See annex 9f (Nwaka S, Widdus R. *The current research-to-development 'hand-off' process for product concept/candidate products and possible improvements in it*).

[4] See annex 9d (Schmid E. *Portfolio management in the pharmaceutical industry*).

Level of portfolio management

A number of times during the workshop, discussions focused on the different levels at which portfolio management could be conducted within the PD PPP field. Portfolio management could in theory be done at several levels by different players:

- Across the various diseases of poverty (neglected diseases) and across PD PPPs, by funders acting in coordination.
- Across a disease area, by a PD PPP.
- Across the array of products being developed by a particular PD PPP.

One of the challenges of operating portfolio management across the various neglected diseases and across PD PPPs would be how to implement the process efficiently to ensure timely and effective decision-making, which would be respected by all parties involved. Similarly it is unlikely that a single PD PPP would ever hold sway across all development in a particular disease area. However, some PD PPPs today chose to prioritize and select candidate products for development in light of those products already under development in their field; thus helping to reduce the development risk within a particular disease/product area.[1] Other PD PPPs are applying the principles of portfolio management to the array of products they are developing or have direct influence over.

The general conclusion of the discussions was that funders need to be in a position to support the portfolio management process and its outcomes but that PD PPPs are best placed to run the portfolio management process. Many individual donors do not have the depth of technical and scientific knowledge needed to choose winners and losers from among dozens of competing proposals. Most PD PPPs have explicit policies affecting portfolio turnover, with 'go-no-go' decisions taken by world-class scientific advisory boards and PD PPP technical staff. Thus the PD PPPs provide a way for funders to 'outsource' these decisions to technical experts.

Scale for portfolio management

Many PD PPPs are still in the early stage of developing their portfolios, falling well below the flow of products that would statistically be required to ensure 'success'. From the work so far and the discussions during the meeting it is not clear what threshold for minimum scale or optimal functioning is required for portfolio management to be most effective. There was concern that to achieve scale there may be incentives to include leads of lesser technical merit or reluctance to kill projects in the pipeline for lack of better alternatives, thus reducing the overall potential for success. However, there was recognition that a rigorous process, with criteria agreed prospectively, can help improve the objectivity and quality of decision-making, one of the cornerstones of the PD PPP model.

To understand effective portfolio management with a smaller number of candidates (as seems a necessity in the vaccine field for practicability), it may be valuable to look at what the biotech field is doing in this area. In the case of some of the vaccine PD PPPs (MVI and IAVI), which have a portfolio of candidates against the same disease target, there may be less opportunity to learn from industry (the norm in industry is to have multiple candidates against different targets). The benefits from a portfolio with multiple candidates focused on the same disease target come more from the lessons and knowledge transfer across the portfolio.

It is also worth noting that in many cases, while a PD PPP may determine which candidates are the most promising to meet a particular need, this does not always mean the PD PPP will be directly responsible for the development of the selected candidate. Depending on the context in which they operate and the availability of suitable partners a PD PPP may outsource either in part or completely the development of the prioritized candidate product(s).

Target product profiles

Establishing agreed target product profiles (TPPs) is a common tool used in portfolio management to facilitate communication and expectation-setting along the development pipeline and to help to ensure that all relevant parties have input (manufacturing, end users, etc.).

In general, TPPs include ideal and minimum criteria across a range of dimensions that reflect the cross-functional nature of product development. The criteria go beyond scientific potential to include usability, manufacturability, costs, time to market and market

[1] See annex 9b (Sander A, Widdus R. *The emerging landscape of public-private partnerships for product development*).

potential. By defining success prospectively, and early in the process, progression or 'kill' decisions are streamlined at a later stage. PD PPPs (in consultation with their disease-control counterparts) are ideally positioned to play a role in developing target product profiles for their diseases. TPPs can be used to solicit submissions in open calls for candidates or as a screening tool for looking at in-licensing opportunities.

Managing the development of the profile and ensuring input from all the relevant stakeholders are almost as important as developing the profile; a good process is the best way to ensure a good profile. The process of portfolio management and TPPs are well established in many big pharmaceutical companies offering another potential area where industry could help with resources or know-how.

Valuing products in a PD PPP environment

In the private sector, products enter the pipeline at all stages of development. Capital markets and financial tools facilitate determination of a 'value' for products and thus allow seamless comparison of in-house candidates and external opportunities. Across the PD PPPs, portfolios of products have evolved very differently, coming from basic research, previously abandoned private sector candidates or existing products being considered for a new use. Ascribing monetary value to these products is not particularly valuable given the relative lack of a commercial market for products in the PD PPP world. Given that the common goal of PPPs is public health impact, it seems desirable that an approach be developed to express the potential benefit of the anticipated products, taking into account factors such as:

- Cost and likelihood of successful development.
- Target population and the fraction likely to be reached.
- Cost of ensuring 'access'.

Funders and portfolio management

PD PPPs have a further challenge when executing portfolio management given the direct involvement of many of the current funders of PD PPPs. A PD PPP that wants to kill a project not only has to say "No" to researchers but also sometimes to funders. In many cases, funders are not currently aligned with a portfolio of products but fund individual products or projects.[1] Many organizations providing funding today and in the future are not going to be familiar with drug development, the long time frames and the high level of failure during development (a 95 per cent failure rate is the norm[2,3]) putting PD PPPs in the role of educator and manager of expectations.

The general conclusion during the discussions was that funders should probably let PD PPPs manage the science advice and the portfolio process.

Open questions

- Are there best practices for successful portfolio management in big pharmaceutical companies and the biotech industry that would be applicable for PD PPPs, including those developing vaccines?
- Are PD PPPs big enough to achieve the benefits of effective portfolio management? At what scale is portfolio management most effective?
- Are funders willing to align themselves with a portfolio of product candidates rather than specific projects?
- Do PD PPPs require specific resources and capabilities to support portfolio management (e.g., portfolio models for vaccine candidates)?

Preparing for access: availability and adoption

No drug, vaccine or device will be effective even if it is affordable and of high quality if it does not reach those for whom it is intended. Ensuring access, availability and wide adoption is as much of a challenge as the development of the technologies themselves. Public health experience has shown that uptake of new technologies is not always automatic (e.g., hepatitis B and antiretroviral drugs).

The term 'access' is often used to describe a variety of different issues associated with the development of products targeting the diseases of the poor, ranging from public policy to end-user product acceptability. While there is no commonly agreed definition for the purpose of these discussions, two broad categories of issues will be considered under the umbrella of access: availability and adoption.

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[1] See annex 9b (op. cit.).

[2] See annex 9a (Towse A, Mestre-Ferrandiz J, Renowden O. *Estimates of the medium-term financial resource needs for development of pharmaceuticals to combat 'neglected diseases'*).

[3] See annex 9l (op. cit.).

The work to ensure access needs to be started in parallel with the product development process to ensure that the demand, public policy, financing and infrastructure are all in place when a product is successfully developed.[1] There was a general feeling that PD PPPs need to embrace these issues but that they may not necessarily be the best group to address all of them directly. However, PD PPPs may be able to play a role in defining the conditions required to support/ensure access.[2] Critical steps in preparing for access (beyond the fundamental tasks of appropriate design for disease-endemic countries and user acceptability) include the development of:

- Ensuring *availability* requires:
  - — Appropriate regulatory approval and licensing infrastructure
  - — Manufacturing capability and sufficient capacity
  - — Logistics and delivery networks in-country.
- Ensuring *adoption* requires:
  - — End-user awareness about the product and its benefits
  - — Effective pricing and financing mechanisms to ensure affordability
  - — Supportive social and policy environment (and the research to generate this).

Planning for availability and adoption will take significant investment, which is often neglected. For example, in the case of vaccines accurate uptake curves based on product profiles and projected prices are required five years before licensure to ensure capital investment in properly sized factories to prevent tragic delays in availability.[3]

At a macro level the leadership in DECs needs to become champions of health issues for long-term successful adoption of these products. Countries where the most progress is being made in tackling diseases of poverty have significant leadership from the top (e.g., introduction of vaccines in Mozambique and the roll-out of new anti-malarial treatments in Zambia).

Open questions

- What role can current funders play in mobilizing required resources to ensure delivery systems are in place?
- Who is best placed to build the evidence to influence policy as these new technologies are developed? What evidence will be required?
- How involved should PD PPPs be in the tasks associated with preparing for access? Who should be taking the lead? If the private/governmental sector is not fulfilling their responsibilities, who can hold them accountable?
- How can the attention of the leaders in disease-endemic countries be captured?

Financing

As one of the chief executive officers of a PD PPP who attended the workshop put it "Our job is balancing time and resources to do whatever is necessary to bring a product to market." Whether done privately or in the public domain drug development is expensive. When we are also talking about enabling access and delivery for these drugs in developing countries where the mechanisms and policy are not yet in place, expected costs rise even higher.

PD PPP needs

A steady flow of funds or a significant amount of money in the bank is important to operate the daily activities of the PD PPPs and give them credibility. One of the most important tasks for PD PPPs is attracting human resources to do the work. Unlike a start-up biotech a PD PPP cannot offer the necessary significant financial incentives like talent stock options, making the stability of funding very important. Having a strong bank balance also helps ensure PD PPPs are taken seriously when they negotiate with potential collaborators from industry. Companies that work with PD PPPs want to know that if they start projects there will be financing to complete them.

One of the challenges faced by PD PPPs is that unlike a venture capital firm which invests in a biotech for an agreed expected return, many of today's funders have not defined what they are looking for when investing (e.g., absolute public health impact versus impact for the poorest social groups). A venture capital firm investing in a start-up biotech would also want a

[1] See annex 9i (op.cit.).

[2] PD PPPs may also be able to work with access PPPs in fields where they have been established.

[3] See annex 9k (Sadoff J. *The Cost of Trials and Manufacturing Process Development for Vaccines*).

good understating of the likely scale and timing of the potential funds required; such clarity is not yet available to funders of PD PPPs.

There was some discussion about the timing with which funds are disbursed to PD PPPs and the merits of incremental year-by-year funding versus lump-sum commitments that represent several years of funding. There was recognition that the larger lump sums bring increased flexibility and credibility but that in practical terms incremental funding was much more likely. It many cases the incremental approach is not very systematic and comes in dribs and drabs from different grants and different funding processes. As the size and complexity of the financial commitments being made by the PD PPPs increases, so too will the importance of understanding the achievements/metrics required for receiving additional support.

Current situation

Based on estimates of funds committed by early 2003, and cost estimates for the portfolio of products underway, the financing shortfall through 2007 for major PD PPPs appears to be at least US$ 1.2 billion and possibly over US$ 2.2 billion, depending on assumptions.[1] There was strong agreement about the severity of the funding gap, if not its exact size, and concerns that the current base of funders may not be sufficient to sustain the existing array of early candidates and PPPs as they mature.

Today's best estimates of the funding gap are based largely on estimates of development costs by phase of development and expected failure rates for different phases of development based on historical experience. In some, possibly most, situations the cost of delivering the drugs could significantly exceed the product development costs. During the meeting a strong desire was expressed to expand this work to provide an even clearer picture of the funding gap. Areas that could benefit from further clarification and inclusion in such an analysis include:

- Attrition rates by phase of development,[2] particularly for newer vaccines.
- Cost of development by stage (see annex 9a).
- Investment in capacity required (e.g., clinical trials, manufacturing facilities, etc.).
- Preparation for access (e.g., research to influence policy, delivery systems, etc.).
- Timing of the required funds.
- Variation in the above factors across drugs, vaccines, diagnostics and other products.

While in-kind contributions are recognized as an important resource to the field that is likely to continue, quantifying their value is particularly hard given the unpredictable and sometimes intangible nature of these contributions.

Broadening the funding base

Today the majority of funding for the PD PPPs comes from bilateral organizations and philanthropic foundations focused on development and public health. In some cases PD PPPs are still supported by a single, or very preponderant funding source. The Bill & Melinda Gates Foundation is the sole or major funder in FIND, MVI and HHVI. The sheer weight of future investment required makes it essential for the field to generate support from beyond these traditional funders, which have many competing demands on their resources. On top of this there is growing concern that the growth of the field is stretching the human resources of both existing funders and the PPPs with the amount of time spent on educating and lobbying for funding. In addition many of these funders are working to meet the needs of getting existing technology to people today.

Broadening the funding base beyond traditional 'development' funders will require a focused advocacy effort for both the PD PPP model and investment in product development. Neither traditional funders nor potential funders have historically invested in this type of product development and may not be able, at this point, to grasp the real significance of candidate failures or the magnitude of the investment required. For many there will be the question of the trade-off between investing in getting existing products to people today and investing in R&D for new products. The increasing use by PD PPPs of more business-case style analysis that starts to look at return on investment (both public health and monetary) will help funders assess these trade-offs. The more sophisticated and practised the PD PPPs become at these analyses, the better they

[1] See annex 9a (op. cit.).

[2] Including differences between small-molecule drug and vaccine development.

will be positioned to obtain financing from any source. While PD PPPs are not the only vehicle for product development, the model appears to be very well adapted to generating in-kind contributions and support from both the private and the public sectors. Analysis by impartial commentators concluded that the PPP approach, while needing some refinements, is currently the main hope for progress.[1]

The good news is that there are still many global players who are not actively supporting investments in product development (e.g., not all members of the G8). However, as discussed earlier, any strategies to increase support will only be successful with clear, simple messages about the benefits and public health outcomes the PD PPPs aim to deliver and why the model is advantageous. For some of the smaller governments and funders, which do not have the capacity to assess each PD PPP investment opportunity, efficient mechanisms to get them involved will be important. Within the private sector there could also be opportunities to get some of the multinational companies involved.

Innovative strategies

Other ways to address the funding gap include exploring other financing mechanisms to attract new funds and looking for potential cost-saving strategies.

Financing

The World Bank's 'Out of the Box' working group[2] has, as part of its remit, been looking at opportunities to leverage the capital markets to attract new funders or optimize existing financial flows.[3] Some of the mechanisms allow funds promised in the future to be brought forward in time (tax exempt debt and securitization); others could bring new capital (project finance and put options[4]). In general, while these mechanisms may be applicable in a small number of situations (e.g., project financing to help enable investment in manufacturing sites), they are unlikely to attract significant amounts of new capital to product development *per se*.

'Pull' mechanisms, including guaranteed purchase, could also benefit the PD PPP field. These mechanisms reduce risk to the developers by providing assurances about the future market for the products under development. Recent work by the Pull Mechanisms Working Group[5] has shown that these mechanisms are legally and practically feasible and enforceable, which will increase their potential as a tool for the market. A point made by several groups at the meeting was that 'pull' mechanisms alone will not be sufficient to tip the balance and open the doors to private investment in these markets.

There was also discussion about the potential to encourage more private sector involvement by reintroducing the profit motive. While this is not a new strategy in itself, some of the drug manufacturer representatives highlighted concerns about possible political and negative public relations ramifications of profiting from diseases affecting the poor.

Cost reduction

With such a large amount of funding required, the obvious question of what opportunities exist to reduce the overall requirements must be explored. One of the drivers of cost in the process of developing and gaining approval for a product is the regulatory environment. There could be opportunities even within the current regulatory framework to reduce the burden on phase III trials and perhaps shift some of the work into a phase IV study so that the costs are only incurred if the product is successful.

With some of the later-stage, larger investments, there may also be opportunities for cost savings from sharing resources or investments across PD PPPs, for example development of clinical trials or manufacturing capacity.[6] Other strategies could involve shifting investments to lower-cost countries. However, there was some concern that benefits might not be that significant; for example, one comparison of manufactur-

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[1] See annex 9l (op. cit.).

[2] Assembled by James Wolfensohn, President of the World Bank, the group consists of senior leaders from industry and the public sector, with particular focus on representation by finance professionals specializing in health care.

[3] See annex 9c (Batson A, Shah R, Gingerich C, Rosenquist JN. *PPPs and product development: Innovative financing opportunities and the need for a 'business case' approach*).

[4] A put option is a contract that gives the holder a right to sell a certain asset to the writer of the option at a specified price up to a specified date.

[5] See annex 9i (Ghosh G. *Emerging lessons in preparing for uptake of new vaccines*).

[6] Shared manufacturing facilities are not a possibility for vaccines as current regulations essentially preclude multiple use factories for large scale production.

ing plant costs bewteen India and New Jersey, USA, suggested less than a 20% saving.[1]

Open questions

- What is the true funding gap? How much is required and when?
- Who are other potential funders and what constraints/goals influence what they can fund?
- Is there more to be done to garner support from the countries for which these products are destined?
- What role can existing funders play to help attract additional funders?
- What is the right funding balance between PD PPPs and other product development models?
- How to ensure balanced funding for research, translation, product development and uptake?

Judging success

Many of the PD PPPs have established a set of internal metrics to monitor their own performance. However, there does not appear to be a set of commonly understood metrics across the field. Two sets of metrics are important: operating metrics to measure internal performance (R&D and value added of PD PPP model); and output metrics to quantify potential public health impacts.

Operating measures could go beyond funds raised and disbursed, and typical R&D metrics to highlight the progress made by PD PPPs on value-added activities. Some of the additional categories could include:[2]

- Building unique capabilities and platforms to attract and select the most promising projects.
- Improving their partners' research capabilities.
- Mobilizing funds in line with portfolio and organizational developments.
- Enhancing knowledge and knowledge dissemination among research partners and the broader public health actors involved in turning new products into health impact.
- Progress towards the target (e.g., relative to a road map).

Clear metrics for the field could benefit the PD PPPs in communicating their performance beyond the current audience. In addition, the cost of assessment and monitoring for both donors and PD PPPs will become substantial without common metrics. For funders in particular, there is a strong desire to have output metrics for the field that allow them to compare investment in PD PPPs with other types of investment. Well-defined and widely utilized metrics will not only serve the funders but if action is taken based upon them, this will help to focus PD PPPs and reinforce the management rigour associated with the model.

Open questions

- What operational metrics are applied by PD PPPs today? For whom? What works?
- What are the best practices from private industry? Could PD PPPs use them?
- How can the value added of PD PPPs be measured or tracked?
- Is there a way to quantify both social demand and scientific maturity to enable comparison across this field and other public health investments?

Role of coordination

PD PPPs and the organizations funding them now constitute an increasingly large group. There appear to be potential opportunities for increased coordination either amongst the funders or the PD PPPs

During the workshop many of the participants expressed the view that coordination would be essential for broadening the funding base for the field. Whether it is the funders or the PD PPPs, working together to develop and deliver a simple set of messages about the PD PPP field will be more effective than a multitude of individual efforts, which may be perceived as competing with one another.

An area that was of particular interest to the PD PPPs was a coordinated effort to address some of the systemwide issues that all PD PPPs now face or will face, but which are too large for an individual PD PPP to tackle alone. Some issues were highlighted, such as regulatory harmonization and simplification, clinical trial and ethical review capacity and investment in delivery infrastructure in disease-endemic countries.

[1] Global Alliance for Vaccines and Immunization 2002. Accelerated introduction of new priority vaccines in developing countries. Prepared for GAVI, the World Bank, and the Bill & Melinda Gates Foundation by McKinsey & Company. 76 pp.

[2] See annex 9e (Pfitzer M. *Demonstrating value: Performance metrics for health product development public-private partnerships*).

However, additional areas would most probably benefit too.

The meeting also discussed the potential benefits of investment in shared resources across the PD PPPs in areas such as data management, intellectual property and regulatory skills. Amongst the PD PPPs, a small group of the better-established organizations are connected to varying degrees with information being shared between executives and, increasingly, their staff members. PD PPPs themselves will need to drive any further coordination or even collaboration amongst them. In general, there were some reservations about how much coordination on core operational activities would be beneficial. There was some concern from the PD PPPs that additional umbrellas organizations could create additional burdens to getting their work done.

Open questions

- How can donors work together to help address some of the systemic challenges facing the field (e.g., regulatory harmonization, public health policies, etc.)?
- What are the best ways for the field to coordinate work on advocacy for the model?
- Should funders coordinate to reduce transaction costs for PPPs and themselves (e.g., independent assessment of PD PPPs, common frameworks for proposals, etc)?
- Would investment in shared resources for the PD PPPs be beneficial or desirable?
- Is there value to having a body that represents the PD PPPs collectively?

Meeting takeaways

- PD PPPs are at present the best approach to development of products to combat diseases of poverty.
- Product development (customer needs and technical development) should remain the core focus of the PD PPPs; other roles will be determined by the context in which they operate.
- Both similarities and differences across PD PPPs needs to be recognized.
- Increased involvement of the disease-endemic countries along the R–D–A continuum is critical to long-term, sustainable product development and adoption of successful products.
- Currently a funding gap for product development in neglected diseases exists; exact funding needs are still not fully known.
- Development of some common operating performance metrics and measures of likely public health impact would be beneficial to PD PPPs and funders.
- Additional sources and mechanisms for funding product development will need to be mobilized; both 'push' and 'pull' mechanisms will be required.
- Mobilizing new sources of funding will require a coordinated effort by current funders and PD PPPs.

Areas for future attention

Roy Widdus and Katherine White

As the global commitment to address the burden of communicable diseases associated with poverty increases, so too does the awareness of the need for new treatments and interventions to address these diseases. To date, the PD PPPs have shown themselves to be the most promising vehicle by which to develop these much-needed tools. The momentum that has developed behind the current array of PD PPPs in the past five years is impressive, but there is more to be done if they are to achieve their full potential and provide the best return on investment.

During the IPPPH workshop in April 2004 a number of areas requiring further attention was identified. Addressing these areas will help ensure the continued progress of the PD PPPs. While the participants came to no specific consensus conclusions about the relative priority of these activities during the workshop, its organizers have solicited further input from the overall meeting co-chairs, the session co-chairs, current funders of the PD PPPs, the PD PPP CEOs and participants from African countries to develop some consensus about the priority areas to be addressed.

The following section represents a synthesis of the input from these groups combined with the discussions during the workshop.

Addressing the following challenges will most likely enhance the probability for ultimate success of the PD PPPs:

- Development of common performance measures.
- Coordination on clinical trial capacity development.
- Harnessing the potential of the disease endemic countries.
- Ensuring financial sustainability of the PD PPPs.
- Communication and coordination.
- Fully recruiting potential industry contributions.

Development of common performance measures

The need for the development and implementation of some commonly recognized, comparable measures by which to assess the performance and progress of the PD PPPs was highlighted at the workshop itself, at the donor consultation associated with the workshop and by many of those involved in the post-workshop consultation.

Recognizing that each of the PD PPPs has a different set of objectives and that these will evolve over time, there was still strong feeling that the benefits of recognized quantitative and qualitative measures of performance would be significant for the PD PPPs themselves, current and future funders of PD PPPs, as well as their potential partners.

Desirable performance measures mentioned during the meeting included:

- Estimates of the potential public health impact and cost-utility of new products
- Quantitative productivity goals
- Measures of PD PPP 'added value' including the effectiveness of their portfolio management approaches for public health outcomes.

Those funding PD PPPs today and in the future will always have their own strategies and preferences for areas of investment (e.g., specific diseases, specific stages of development, etc.). However, they all need to be able to evaluate the performance of their investments. A common set of measures will help ensure an objective evaluation of how well an organization is performing against specific goals and relative to other similar types of organization. Likewise for PD PPPs, the opportunity to develop a track record may also facilitate longer-term financial commitments from funders as investments are made based not just on achievement

of milestones but also improvements in performance. The availability of public information and the development of a performance track record will also help industry partners, researchers and other stakeholders. Strong indicators will provide valuable data with which they can make the case for getting involved with a specific PD PPP.

Estimates of potential public health impact of new products start within the burden of the disease targeted. However, they also take into account the probability of success in product development *per se*, the time to success and the subsequent time to wide application. They need to incorporate some estimate of the fraction of the theoretical target population that would actually be reached given the likely delivery systems, and the efficacy of the intervention. Combined with the costs of product development and the costs of application, such cost-utility measures would provide investors additional information to help inform decisions. Admittedly, such estimates incorporate projections that are often uncertain but the effects of these on the robustness of conclusions can be determined by sensitivity analyses using a range of plausible predictions.

Such analyses of potential public health impact have been used by the National Institute of Allergy and Infectious Diseases, for vaccines[1,2] and could be easily extended to other products.

Productivity goals do not necessarily need to incorporate or assume guarantees of success in delivering new products. Where there is higher lack of certainty about scientific success (e.g., some 'first-in-class' vaccine development efforts) productivity goals can be framed in terms of process measures (e.g., moving *x* candidates from development stage *b* to development stage *e*). Quantitative productivity goals will enable PD PPPs the better to calculate and negotiate for the funding they need to pursue their mission. Without a clear sense of what will be attempted, funding will be more difficult to negotiate and evaluate.

Some meeting participants informally expressed reservations about the feasibility and use of common performance measures; they argued that the activities of each PD PPP were so different scientifically that no common measures could be found. Some were also apprehensive about the use of such measures for comparison.

Marc Pfitzer[3] discussed the 'value' that PD PPPs provide for funders. This value actually lies at levels other than the strictly scientific aspect of product development, where most of the variation between different disease/product targets actually occurs. Such value is represented in the quality of the scientific advice brought to bear on decisions, the quality of project oversight and coordination across multiple players, in the rigorous execution of project management approaches and in cost controls. PD PPPs need to consider their value-added contributions. If PD PPPs themselves define the way in which their approach adds value, they will be contributing to the creation of common performance measures.

This may require extensive consultation to achieve agreement on meaningful approaches, but eventually should help the ventures as well as their funders.

Related to added value is the relatively unquantified area of portfolio management approaches for public health goals. As pointed out by Towse and colleagues,[4] data and techniques for commercial portfolio management are mostly based on drug candidate attrition rates. Further work specifically for vaccine candidates would benefit a range of PD PPPs addressing vaccines.

PD PPPs apprehensive about use of common performance measures should recognize that comparisons are already being made now by measures that are not identified explicitly. They will be better able to make their case if funders are using specific criteria for comparisons.

Successful establishment and development of such metrics will take time and require the buy-in and long term commitment of both the PD PPPs and their current funders. The challenge for funders (and possibly management consultants or other impartial actors) is to define common performance measures that can be used legitimately across different PD PPPs. Care will also need to be taken to ensure that common performance measures are used appropriately, and that legitimate reasons for differences, e.g., differences in

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[1] Institute of Medicine, 1986. *New Vaccine Development: Establishing Priorities.* Volume 1: Diseases of Importance in the USA. 458 pp.; Volume 2: Diseases of Importance in Developing Countries. 432 pp. National Academies Press, Washington, DC.

[2] Institute of Medicine, 1999. *Vaccines for the 21st Century: A tool for decision making.* 476 pp. National Academies Press, Washington, DC.

[3] See annex 9e (op. cit.).

[4] See annex 9a (op. cit.).

the level of scientific challenge resulting from disease/product choice, are taken into account.

Coordination on clinical trial capacity development

As many of the PD PPPs make progress and bring candidates successfully into the later stages of development, the need for clinical trial capacity in DECs has become increasingly urgent. Phase III clinical trials are one of the most critical and expensive stages of the development process (Di Massi et al. estimates 30 per cent of successful drug products' development costs are incurred during phase III trials[1]), and this is probably higher for vaccines.

Today, despite the many groups working to develop clinical trial sites and the predicted demand for such sites, there is still insufficient capacity and overall capability in disease-endemic countries to meet existing demand. This shortage of capacity will lead to undue competition for sites and costly delays to the clinical development of these much-needed products unless it is addressed.

Increased coordination among funding agencies and product developers for 'neglected diseases' will help ensure funds are invested efficiently and in such a way as to ensure the capacity can be sustained. Such coordination may involve groups working together across multiple dimensions including the development of training programmes, sequencing and timing of trials, development of sites and/or establishment of multi-trial sites. From discussions with the African participants they may be well placed to take the lead in coordinating across the PD PPPs (see discussion below).

If, wherever possible, PD PPPs adopted common trials data management systems, then training, trials implementation and analysis would be facilitated.

Without close collaboration between the agencies currently developing sites, the PD PPPs and resources in the disease-endemic countries, it is highly unlikely that the urgently needed trial capacity will be available in time.

Harnessing the potential of disease-endemic countries

During the meeting and in follow-up discussions, there was strong agreement about the importance of legitimate involvement of the various constituents from the disease-endemic countries. While there are many examples within PD PPPs of DEC scientists and institutions playing critical roles, there still are additional opportunities for increased involvement and needs in these countries, e.g., regulatory capacity strengthening related to rapid uptake. Some opportunities may be immediate, but leveraging the full potential that the DECs have to offer will require investment in new capacity. The African participants highlighted three areas of opportunity (and these are likely to be explored further by them in a workshop scheduled for August 2004).

Clinical trial capacity development

While no specific resources are available in Africa today to assist with the general development of clinical trial sites, many of the activities required to provide such service could, with some targeted training and system development, be handled by personnel trained and living in Africa.

R&D on products from traditional African medicines (TAM)

Throughout Africa there is widespread use of traditional medicinal plants as health measures by traditional health practitioners.[2] While not developed under recognized regulatory processes, the numerous plant species with potential medicinal used in TAMs could be a valuable source of product ideas and leads. Networking institutions in the field and linking to pharmaceutical development expertise would be useful.

African Scientific and Technical Review Committee

Today product developers make trial applications through bodies in Europe and the United States. As a result IRB members are trained in line with European and US ethics and standards. While these standards are important, so too are experience and credibility with the African communities. Within Africa there are currently enough individuals with sufficient experience of both cultures to enable the establishment of an African Scientific and Technical Review Committee which could help improve the smooth running of tri-

[1] Di Massi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *Journal of Health Economics*, 22(2003) 151–185.

[2] See annex 11 (Kimanani E, Akanmori B, Gamaniel K, Inyang U, Kilama J, Kitua A, Leke R, Pallangyo K. *Consolidation of the Private Partnership For Product Development: Africa's Role*).

als in Africa. The 'critical mass' available at a regional level could help train and develop capacity including that for **regulatory approval** in the individual major countries of the region.

If the full potential of the DECs is brought to bear on the challenges faced by the PD PPPs, there is a much higher likelihood that these countries will feel truly involved. They will thus take greater ownership of the end products that are developed and will contribute both in-kind and financially to their development and rapid utilization.

Ensuring financial sustainability of the PD PPPs

Despite significant success in raising and mobilizing funds the PD PPPs are still under-resourced. While the exact size and timing of future funding required by the PD PPPs is difficult to ascertain precisely, there was strong agreement about the severity of the funding gap and concerns that the current base of funders is not sufficient to sustain the existing field.

Maintaining the current level of funding and attracting additional support beyond the traditional 'development' funders will require better understanding of the size and timing of the current funding gap and a clear case for the benefits of investment in product development and the PD PPPs. For some of the smaller governments and potential funders, finding an efficient way to get them involved will also be critical as they do not have the capacity to individually assess all PD PPP investment opportunities.

Both the industry executives and current funders of the PD PPPs will need to work together if they are to develop effectively and deliver clearly the required messages about the potential value of investing in the PD PPPs.

Communication and coordination among players in the research–development–access (R–D–A) continuum

It became apparent during the IPPPH's London workshop that some level of contact among different players in the R–D–A continuum exists, e.g., occasional contacts between PD PPPs. However, it is unrealistic to believe that the current level of communication and coordination is optimal. Indeed, the meeting was the first time that the PD PPP 'executives' and their major funders had met to share information and viewpoints. Enhanced communication and coordination are needed both across different product development efforts and also along the R–D–A continuum.

While additional coordination should improve overall efficiency and prospects for success, it should be seen as a means to an end, not a goal in its own right. Proposed information exchange and coordination activities should be considered carefully so as not to impose unnecessary burdens on already busy individuals and ventures.

PD PPPs should consider where there is advantage in:

- Information sharing, e.g., on deal making and/or intellectual property management.
- Coordinated action, e.g., possibly on common systems for clinical trials data management.
- Collective advocacy, e.g., for attention to product development to achieve the Millennium Development Goals.
- Collective action for resolution of common problems, e.g., strengthening of regulatory capacity in disease endemic countries.
- Development of methods (especially for vaccines) of portfolio management based on likely public health benefits.

Funders should continue dialogue on:

- Their desire for common performance metrics
- Opportunities to coordinate funding
- Strategies to expand the pool of funding.

Players *along* the R–D–A continuum for particular diseases should consider what communications and coordination vehicles would be useful:

- To ensure that necessary information for policy decisions (e.g., on public health utility) is developed in a timely fashion (not sequentially/subsequently to product development itself)
- To best ensure anticipatory action (e.g., estimating demand, ensuring financing and strengthening delivery systems for rapid uptake) is planned and undertaken in a timely fashion.

One facet of coordination along the R–D–A continuum that particularly deserves additional attention is the translation of concepts relevant to combating 'neglected diseases' from basic research to the status of candidate products. This 'translational research' is

of concern to both basic research funders who want to see results in terms of health benefits, not only scientific knowledge, and to PD PPPs who need to be assured of an adequate flow of scientifically valid candidate products into their portfolios.

Although not cited by any PD PPP as their major current obstacle, it is a persistent concern, particularly for fields that have been relatively more neglected (e.g., tuberculosis and uniquely tropical diseases like Trypanosomiasis). Hence it deserves attention now to enhance the prospects of return on basic research investment and long-term PD PPPP success. A study of current efforts in translational research and workshops to enhance coordination between basic research and PD PPPs (or some other means to achieve this goal) is warranted.

Fully recruiting potential industry contribution

Many participants in the IPPPH's London meeting expressed the view that – overall – the experience and expertise of pharmaceutical companies, particularly the larger ones, could and should be more fully recruited to the 'enterprise' of product development for diseases associated with poverty. Contributions from industry could assist at various levels: the individual project level; overall portfolio PD PPP management; and in funders' assessments of individual PPP functioning.

Decisions about different sorts of engagement will be taken at the individual company level, and often on a case-by-case basis in response to specific requests. Therefore, it is difficult to devise a general strategy for enhancing the engagement of pharmaceutical companies with PD PPPs and their funders. Suggestions are made in the following section (Moving forward).

Notwithstanding the situation described above, the potential for instituting exchange schemes between public/governmental sector, pharmaceutical companies, and the not-for-profit sector should be explored as a means of improving understanding and knowledge transfer.

Moving forward

Roy Widdus

The workshop convened by IPPPH in April 2004 represents the first time representatives of all major not-for-profit ventures for 'neglected disease' product development and their principal funders had ever assembled to discuss issues of common interest in addressing diseases associated with poverty.

While the field is diverse, the *Meeting summary* and the emerging themes in *Areas for future attention* identified a range of issues where further discussion among various players will enhance the prospects for success. The best mechanisms for facilitating these further discussions are also in the process of definition.

Donor coordination

The principal PD PPP funders which had participated in planning the workshop (the Bill & Melinda Gates Foundation, the UK Department for International Development, the Rockefeller Foundation and the Wellcome Trust) convened after the workshop a small consultation among current PD PPP funders to discuss issues of shared concern. Conclusions of that meeting are provided in the Annexes in the full meeting report.[1]

As of the time of publication, this Donor Consultation Group is working to define an agenda of work to address their concerns.

To contact the group, write to Dr Charles Gardner, Associate Director, Health Equity, The Rockefeller Foundation, at <gardner@rockfound.org> or Katherine White at <kawhite@kawhiteconsulting.com>.

[1] See annex 10 (*Donor Consultation on Policy and Programming for PD PPPs, 16 April 2004, The Wellcome Trust, London, UK*).

Coordination among PD PPPs

As of publication, the Initiative on Public-Private Partnerships for Health and its parent organization, the Global Forum for Health Research, are assessing its future role. Information on coordination among PD PPPs will be posted on the IPPPH website and can also be obtained from the major PD PPPs.

For further information, visit the IPPPH website or email the Secretariat at info@ippph.org.

Coordination among disease-endemic country researchers and policy-makers regarding capacity strengthening

Subsequent to the London workshop, African participants convened a workshop on 30 August to 1 September 2004 in Nairobi, Kenya to discuss their contributions to product development for diseases endemic in sub-Saharan Africa. It is planned to post the report of the meeting on the IPPPH and TDR websites with contact details for sources of further information. A plan for activities under the umbrella of the African Health Research Forum is under development.

Coordination along the research-development-access continuum

Coordination among players and funders along the R–D–A continuum is probably organized most easily on a disease-oriented basis. Hence, the IPPPH Secretariat will be exploring with other parties the level of interest in periodic meetings of relevant players. IPPPH will, therefore, consult with the general coordination secretariats for various diseases, including those for the Stop TB Partnership, the Roll Back Malaria Partnership and the HIV/AIDS and Communicable Diseases Departments of the World Health Organization. For

further information, see the IPPPH website or contact the Secretariat via <info@ippph.org>.

Recruiting potential industry contributions

As noted above, pharmaceutical companies will most probably make decisions on engagement in different aspects of developing products for disease associated with poverty at individual company level, or even a case-by-case basis, as their in-house R&D activities and policies/philosophies vary.

Given this situation, proposing an overall monolithic approach to more fully recruiting industry expertise may not be as useful as pursuing their fuller involvement in the various forums noted above, particularly the proposed disease-specific discussions that will bring together different players along the research-development-access continuum.

Post-workshop consultation
on *Meeting summary* and *Areas for future attention*

All PD PPPs were given the opportunity to respond to drafts of the *Meeting summary* and *Areas for future attention* before their finalization. Significant contributions to or comments on the *Meeting summary* and/or *Areas for future attention* were received from the following meeting participants:

Patricia Danzon, The Wharton School, University of Pennsylvania, USA (Session Co-chair)

Charles Gardner, The Rockefeller Foundation, USA (Co-organizer)

Michael Harper, Consortium for Industrial Collaboration in Contraceptive Research/Contraceptive Research and Development Program (CICCR/CONRAD)

Jane Haycock, Department for International Development, United Kingdom (Co-organizer)

Hannah E. Kettler, Bill & Melinda Gates Foundation, USA (Co-organizer)

Ebi Kimanani, International Biomedical Research in Africa (IBRIA), Kenya [On behalf of the African meeting participants, namely: Rose Leke (Cameroon), Bartholomew Akanmori (Ghana), Uford Inyang (Nigeria), Andrew Kitua (Tanzania), Kisali Pallangyo (Tanzania), and John Kilama (Uganda)]

Andrew Y. Kitua, National Institute for Medical Research (NIMR), Tanzania

Adel Mahmoud, Merck Vaccines, USA (Meeting Co-chair)

Sigrun Møgedal, NORAD, Norway (Meeting Co-chair)

Melinda Moree, Malaria Vaccine Initiative, USA

Gwynne Oosterbaan, Global Alliance for Tuberculosis Drug Development (TB Alliance), USA

Sue Perl, Consultant to The Rockefeller Foundation, United Kingdom (Co-organizer)

Adrian Towse, Office of Health Economics, UK

Annexes

ANNEX 1

Agenda

Workshop on 'Combating Diseases Associated with Poverty: Financing Strategies for Product Development and the Potential Role of Public-Private Partnerships'

15–16 April 2004

DAY ONE	THURSDAY 15 APRIL 2004
8.30 am–9.00 am	Registration for badges (Reception Hall)
SESSION I	**Purpose:** To introduce the issues to be addressed in the workshop and particularly, in the keynote address, to identify the expertise that is essential for product development, to identify who possesses these skills, and to provide an overview of how product development (PD) public-private partnerships (PPPs) recruit these in the interests of global public health.
9.00 am–9.10 am	**Welcome** ■ Mark J. Walport, Director, Wellcome Trust Introduction of Meeting Co–chairs: ■ Adel Mahmoud, Merck Vaccines (Merck & Co., Inc.), USA ■ Sigrun Møgedal, Norad, Norway
9.10 am–9.20 am	**Aims of the workshop** ■ Roy Widdus, Initiative on Public-Private Partnerships for Health, Geneva, Switzerland
9.20 am–9.30 am	**Overview of programme** ■ Co-chairs
9.30 am–10.30 am	**Linking private sector expertise in product development with public sector goals to combat global health problems** ■ Gail H. Cassell, Ph.D., Eli Lilly and Co., USA *Questions and discussion*
10.30 AM–11.00 AM	COFFEE/TEA BREAK (FRANKS ROOM)
SESSION II	**Purpose:** The session will clarify the benefits of pursuing a portfolio of candidate products, why it is appropriate to development of products to combat 'neglected' diseases, how the various not-for-profit PD ventures differ in scope and approach, and how it is possible to measure their added value.
11.00 am–12.30 pm	Chair: ■ Gill Samuels, Pfizer Global Research and Development, UK **Panel: Portfolio management in pharmaceutical companies and PD PPPs** – based on background papers, with authors on the panel responding to questions and with general discussion. ■ Portfolio management in the pharmaceutical industry ■ The emerging landscape of pubic-private partnerships for product development ■ Demonstrating value: Performance metrics for health product development public-private partnerships *Questions and discussion*
12.30 PM–1.30 PM	LUNCH (FRANKS ROOM)
SESSION III	**Purpose:** To examine the specific role of PD PPPs and that of other necessary other players in the chain from 'upstream' basic research through clinical trials to 'downstream' uptake and widespread product use.
1.30 pm–3.30 pm	Co-chairs: ■ John La Montagne, National Institutes of Health, USA ■ Andrew Kitua, National Institute for Medical Research, Tanzania

Panel: The role of PD PPPs and the environment necessary for their success – based on background papers, with authors on the panel responding to questions and with general discussion.

- The emerging landscape of public-private partnerships for product development
- The current research-to-development 'hand-off' process for product concepts/candidate products and possible improvements in it
- Ethical review capacity: Country needs, role and responsibility of partners and researchers
- Current status of clinical trials capacity in Africa
- Emerging lessons in preparing for uptake of new vaccines

Questions and discussion

3.30 PM–4.00 PM COFFEE/TEA BREAK (FRANKS ROOM)

SESSION IV

4.00 pm–6.00 pm

Purpose: To examine the funding needed for product development, the needs of PD PPPs themselves, plus the possible alternatives to such ventures and their costs

Chair:

- Patricia Danzon, University of Pennsylvania, USA

What is the current financial situation for PD PPPs using the portfolio management approach? – based on a background paper.

- Adrian Towse, Office of Health Economics, UK

Panel: Financial aspects of product development for neglected diseases – based on above presentation and background papers, with authors on the panel responding to questions and with general discussion.

- Revising current predictions of PD PPP needs
- Requirements for vaccine product and field site development at a licensure standard
- What are the alternative approaches for 'neglected' product development and their costs?

Questions and discussion

END OF DAY ONE

6.30 PM–RECEPTION-DINNER

The Wellcome Trust

- Guest Speaker: Gordon Conway, President, The Rockefeller Foundation

DAY TWO **FRIDAY 16 APRIL 2004**

8.45 am–9.00 am

Summary of conclusions from Day One

Co-chairs

SESSION V

9.00 am–10.30 am

Purpose: To assess the possibilities for financing for product development from non-traditional sources

Chair:

- Jane Haycock, DFID, United Kingdom

Possible innovative approaches to funding product development for neglected health problems? – based on above presentation and background papers, with authors on the panel responding to questions and with general discussion.

- Innovative financing approaches for 'neglected' product development
- The possibility of tapping major financial flows to disease-endemic countries
- The need for a 'business case' approach

Questions and discussion

10.30 AM–11.00 AM COFFEE/TEA BREAK (FRANKS ROOM)

SESSION VI

11.00 am–12.45 pm

General discussion: What are the remaining questions?

Meeting Co-chairs

- Adel Mahmoud, Merck Vaccines (Merck & Co., Inc.), USA
- Sigrun Møgedal, Norad, Norway

12.45 pm–1.00 pm

Discussion for all participants

1.00 pm

Establishment of Follow-up Monitoring Group

CLOSURE

ANNEX 2

List of participants

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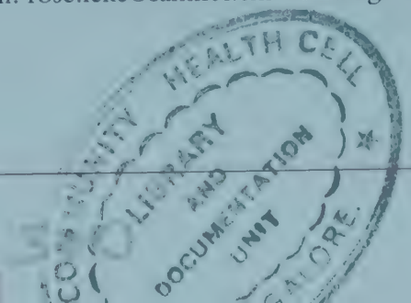

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ANNEX 3A

Background on the product development public-private partnerships under consideration

In the last decade, there has been a significant expansion of so-called 'public-private partnerships' (PPPs) addressing the health problems of low- and middle-income countries (LMICs).[1] The Initiative on Public-Private Partnerships for Health (IPPPH) has identified almost 100 such partnerships which include significant involvement of pharmaceutical or other health product companies. These can be grouped according to their principal purpose as follows:

- Generating basic knowledge/research
- Product development (PD)
- Improvement of access to health products ('access' PPPs)
- Global coordination mechanisms including funding vehicles
- Strengthening of health services
- Public education and advocacy
- Regulation, quality assurance and standards

Figure 1 below shows the rise over a period of 30 years in the overall field and specifically for PD PPPs, 'access' PPPs and global coordinating mechanisms.

In Appendix A, IPPPH lists partnerships in particular categories. Some have ancillary as well as principal functions. (See also: www.ippph.org)

Some **product development** partnerships (PD PPPs) are historical. Among those currently operating, a rough distinction based on general strategy can be made which helps in keeping the upcoming workshop manageable and focused on broad strategic issues.

Some PD PPPs, as a deliberate strategy, opt to foster the simultaneous development of a number of candidate products and chose these by surveying their chosen field. In its most rigorous implementation this portfolio management approach mimics that used in the pharmaceutical industry. Many PD PPPs planning to utilize a portfolio approach are at an early stage of development.

The strategic starting point for other PD PPPs is a particular candidate product (or a very small number of these). IPPPH refers to these partnerships as project-based PD PPPs.[2] Portfolios are obviously built up of individual projects, but some projects are pursued independently (see Appendix B).

The upcoming workshop concentrates on those PD PPPs strategically focused on a portfolio of candidate products.

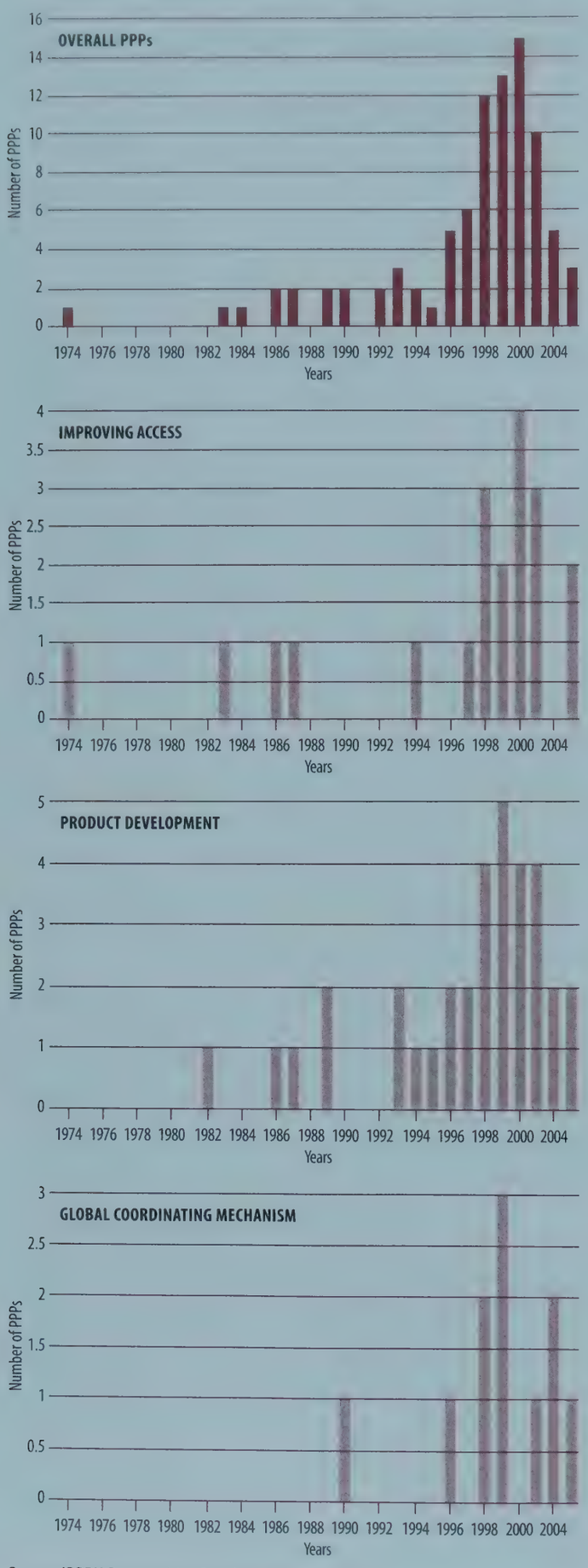
NB. IPPPH recognizes that these distinctions are somewhat subjective, but the multiple candidate/portfolio approach seems to be emerging as a favoured approach that guards against the well known statistical risks of failure inherent in the individual candidate approach.

IPPPH also recognizes that the information gathering and analysis conducted for this meeting did not necessarily cover all the portfolio-based PD PPPs that probably should be included. Apologies are offered where necessary and those omitted are invited to supply the information that will permit

[1] A widely accepted and consistently used definition of public-private partnerships for health remains elusive. The term is sometimes used (perhaps inappropriately) to cover the increase in private sector delivery of health services (the rules for which are solely government controlled) and also (more appropriately) for action for health in LMICs by non-health sector businesses (see Widdus, R. Public-private partnerships need thoughtful consideration. *Bulletin of the World Health Organization* 2003, 81(4) 235).

[2] Project-based PD PPPs also vary considerably. Some focus on essentially proven technologies (e.g., Meningitis A Vaccine Project). Others in the early stages of product development – like the early candidates in portfolios – have a high statistical chance of failing.

Figure 1. PPPs by type of approach between 1974 and 2003



Source: IPPPH Partnerships Database: www.ippph.org

them to be included in future attempts to create comprehensive categories of such ventures.

Appendix C contains abstracts on each of the PD PPPs considered to fostering a range/portfolio of candidate products (for more details, see Partnership Database at: www.ippph.org). A description of BIO Ventures for Global Health is included (Appendix C), as this was emerging as the meeting was planned. It is not, however, included in the analyses conducted for the meeting (e.g., Towse et al, Annex 9a; Sander and Widdus, Annex 9b) as it was not fully operational at that time.

Appendix D contains some examples of project-based PD PPPs.

The background papers by Sander and Widdus (Annex 9b) and Towse et al (Annex 9a) give details of the variations among the PD PPPs under consideration.

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APPENDIX A

Public-Private Partnerships for health in low- and middle-income countries by principal function

Generating basic knowledge/research

Single Nucleotide Polymorphisms Consortium Ltd (SNP)

Product development

Action TB Programme (ATBP) (Historical)
Aeras Global Tuberculosis Vaccine Foundation (Aeras)
Artesunate Suppository for Emergency Treatment of Severe Malaria (Artesunate)
BIO Ventures for Global Health (BVGH)
Consortium for Industrial Collaboration in Contraceptive Research (CICCR)
Contraceptive Research and Development (CONRAD)
Dengue Vaccine Project (DVP)
Drugs for Neglected Diseases *initiative* (DNDi)
European Malaria Vaccine Initiative (EMVI)
Foundation for Innovative New Diagnostics (FIND)
Gates Foundation/University of North Carolina Partnership for the Development of New Drugs (GFUNC)

Global Alliance for TB Drug Development (TB Alliance)
Global Microbicide Project (GMP)
Human Hookworm Vaccine Initiative (HHVI)
Infectious Disease Research Institute (IDRI)
Institute for OneWorld Health (IOWH)
Intercompany Collaboration on AIDS Drug Development (ICCADD) (Historical)
International AIDS Vaccine Initiative (IAVI)
International Partnership for Microbicides (IPM)
Japanese Pharmaceutical, Ministry of Health, WHO Malaria Drug Partnership (JPMW)
LAPDAP Antimalarial Drug Development (LAPDAP)
Lassa Fever Initiative (LFI)
Malaria Vaccine Initiative (MVI)
Medicines for Malaria Venture (MMV)
Meningitis C Vaccine Development and Supply in the UK (Historical)
Meningitis Vaccine Project at WHO/PATH (MVP at PATH)
Microbicides Development Programme (MDP)
Norplant, Development of (ND) (Historical)
Pediatric Dengue Vaccine Initiative (PDVI)
Pneumococcal Vaccine Accelerated Development and Introduction Plan (PneumoADIP)
Syringes – Autodestruct, Development of (Historical)
Tropival
Tuberculosis Diagnostic Initiative (TBDI) (Historical)
Vaccine Vial Monitors (VVM), Development of (Historical)

Improvement of access to health products

Accelerating Access Initiative to HIV Care (AAI)
African Programme for Onchocerciasis Control (APOC)
Children's Vaccine Programme at PATH (CVP at PATH)
Concept Foundation (FC)
Diflucan Partnership Program (Diflucan)
Eli Lilly Multi-Drug Resistant Tuberculosis Partnership (MDR-TB)
GlaxoSmithKline African Malaria Partnership (GSK-AMP)
Global Alliance for the Elimination of Lymphatic Filariasis (GAELF)
Global Alliance to Eliminate Leprosy (GAEL)
Global Guinea Worm Eradication Program (GWEP)
Global Polio Eradication Initiative (GPEI)
International Trachoma Initiative (ITI)
Malarone Donation Program (Malarone) (Historical)
Maternal and Neonatal Tetanus, Global Elimination of (MNT)
Mectizan Donation Program (Mectizan)
Mother-to-Child-Transmission-Plus Initiative (MTCT-Plus)
MSF Campaign for Access to Essential Medicines
NetMark PLUS, a Regional Partnership for Sustainable Malaria Prevention (NetMark PLUS)
Onchocerciasis Control Programme in West Africa (OCP) (Historical)
Oral Rehydration Salts (ORS) Commercialization in Bolivia (Historical)
Praziquantel Manufacturing Project (Historical)
UNAIDS Anti-Retroviral Drug Access Programme (UNAIDS-Industry) (Historical)
UNFPA Contraceptives Access Project (UNFPA/Industry)
Viramune® Donation Programme (VDP)
WHO Programme to Eliminate Sleeping Sickness (WPESS)
WHO/Novartis Coartem® (Coartem)

Global coordinating mechanisms including funding vehicles

Children's Vaccine Initiative (CVI) (Historical)
Global Alliance for Improved Nutrition (GAIN)
Global Alliance for Vaccines and Immunization (GAVI)
Micronutrient Initiative (MI)
Roll Back Malaria Global Partnership (RBM)
Safe Injection Global Network (SIGN)
Stop TB Partnership (Stop TB)
The Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund)
Vaccine Fund (VF)
Vision 2020 (V2020)
Vitamin A Global Initiative (VITA)

Strengthening of health services

African Comprehensive HIV/AIDS Partnerships (ACHAP)
Alliance for Health Policy and Systems Research (AHPSR)
Global Campaign for Microbicides (GCM)

Global Elimination of Trachoma, Alliance for the (GET 2020)
International Partnership Against Aids in Africa (IPAAA)
Multilateral Initiative on Malaria (MIM)
Secure the Future (SF)
Step Forward Program (SFP)
Strategies for Enhancing Access to Medicines (SEAM) at Management Sciences for Health (MSH)

Public education and advocacy

Alliance for Microbicide Development (AMD)
Corporate Council on Africa (CCA)
Global Business Coalition on HIV & AIDS (BGC)
Global Public-Private Partnership for Hand Washing with Soap (GPHW)
Health InterNetwork (HIN)
Hope for African Children Initiative (HACI)
International Programme on Chemical Safety (IPCS)
Vitamin A Global Initiative (VITA)

Regulation, quality assurance and standards

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
Global Reporting Initiative (GRI)
Pharmaceutical Security Institute (PSI)
WHO-Pharmaceutical Industry Associations-NGO Anti-Counterfeit Drug Initiative (ACDI)

APPENDIX B

Product development public private partnerships

Multi-candidate/portfolio-based PD PPPs for neglected diseases

Aeras Global Tuberculosis Vaccine Foundation (Aeras)
BIO Ventures for Global Health (BVGH)
Drugs for Neglected Diseases *initiative* (DNDi)
European Malaria Vaccine Initiative (EMVI)
Foundation for Innovative New Diagnostics (FIND)
Global Alliance for TB Drug Development (TB Alliance)
Global Microbicide Project (GMP) (more data being sought)
Human Hookworm Vaccine Initiative (HHVI)
Institute for OneWorld Health (IOWH)
International AIDS Vaccine Initiative (IAVI)
International Partnership for Microbicides (IPM)
Malaria Vaccine Initiative (MVI)
Medicines for Malaria Venture (MMV)
Microbicides Development Programme (MDP)
Pediatric Dengue Vaccine Initiative (PDVI)
Pneumococcal Vaccine Accelerated Development and Introduction Plan (Pneumo-ADIP)
Rotavirus Vaccine Accelerated Development and Introduction Plan (Rotavirus-ADIP)
South African AIDIS Vaccine Initiative (SAAVI)

Examples of project-based PD PPPs for neglected diseases

Artesunate Suppository for Emergency Treatment of Severe Malaria (Artesunate)
Dengue Vaccine Project (DVP)
Gates Foundation/University of North Carolina Partnership for the Development of New Drugs (GFUNC)
Infectious Disease Research Institute (IDRI) (more data being sought)
Japanese Pharmaceutical, Ministry of Health, WHO Malaria Drug Partnership (JPMW) (more data being sought)
LAPDAP Antimalarial Drug Development (LAPDAP)
Meningitis Vaccine Project at WHO/PATH (MVP at PATH)
Lassa Fever Initiative (LFI) (In early development, therefore uncertain)

NB. Each of the projects in portfolios also represents an individual project-based PD-PPP.

PD PPPs for other health problems

Consortium for Industrial Collaboration in Contraceptive Research (CICCR)
Contraceptive Research and Development Program (CONRAD)

Historical PD PPPs for neglected diseases

Action TB Programme (ATBP)
Meningitis C Vaccine Development and Supply in the UK (MCVD)
Norplant, Development of (ND)
Syringes – Autodestruct, Development of
Tuberculosis Diagnostic Initiative (TBDI)
Vaccine Vial Monitors, Development of (VVM)

APPENDIX C

PD PPPs planning to foster a range of candidate products

Aeras Global TB Vaccine Foundation (Aeras)

The Aeras Global TB Vaccine Foundation (formerly known as the Sequella Global Tuberculosis Foundation) was founded in 1997 to help develop new concepts and tools to control the global TB epidemic. In 1999 the Foundation received a five-year, US$25 million grant from the Bill & Melinda Gates Foundation to fund the TB Vaccine Collaboration. The organization now focuses exclusively on developing new vaccines against tuberculosis and ensuring that they are distributed to all who need them. Major funding comes from the Bill & Melinda Gates Foundation. Aeras is the only organization solely dedicated to developing a better way to vaccinate against TB. Working in collaboration with individual scientists, academic institutions, industry and government agencies in the United States and Europe, as well as South Africa and other developing countries, Aeras aims to bring several of the leading TB vaccine candidates to Phase I, II and III clinical testing over the next decade and to license and manufacture at least one new TB vaccine for worldwide distribution within 10 years.

BIO Ventures for Global Health (BVGH)

BIO Ventures for Global Health (BVGH), launched in June, 2004, was formed to accelerate the development, distribution and accessibility of biotechnology products that address the world's most devastating and neglected diseases. Spun out the Biotechnology Industry Organization (BIO) with initial support from the Bill & Melinda Gates Foundation and Rockefeller Foundation, BVGH is taking a market-based approach to attract biotech innovators to tackle these global health challenges. The organization is premised on three beliefs:

- Biotech innovators have the tools, development expertise and product focus to develop much-needed products for these populations;
- These companies can and will take on these challenges if the market incentives are right; and
- Sufficient market incentives must be in place to attract quality innovators.

Over the next year, BVGH is embarking on two complementary and highly leveraged activities that encourage the private sector to invest their own resources toward global health R&D. First, BVGH is developing a series of product specific business cases to identify viable market opportunities where they exist and map regulatory, licensing and distribution strategies to get successful products to those that need them. Second, BVGH will build industry and donor support for advanced markets or other incentive mechanisms necessary to supplement insufficient markets. BVGH publishes the quarterly *BVGH Report* and maintains www.bvgh.org as a resource for all innovators interested in global health product development.

Drugs for Neglected Diseases *initiative* (DNDi)

Launched on 3 July 2003, DNDi is a new not-for-profit drug research organization, with a secretariat based in Geneva, Switzerland. This new PPP is the first of its kind to focus exclusively on some of the world's most neglected diseases: human African trypanosomiasis (sleeping sickness), leishmaniasis and Chagas disease. DNDi will engage in targeted drug R&D for the most neglected diseases. It plans to spend around US$250 million over the next 12 years to develop six or seven new drugs. It will also encourage the creation of global networks of research facilities and will help strengthen their research capabilities.

European Malaria Vaccine Initiative (EMVI)

EMVI is an international programme of the European Commission and Member States of the European Union (EU)established in 1998 at the Centre for International Health, University of Bergen, Norway. It has secretariats in Copenhagen, Denmark and Paris, France. EMVI's mission is to contribute to the global efforts to control malaria by providing a mechanism for accelerated development and clinical trials of malaria vaccines in both Europe and developing countries, and by promoting affordability and accessibility of malaria vaccines in developing countries. EMVI provides a mechanism to:

- facilitate concerted interaction between a European Commission core activity and EU Member States' investments
- accelerate the process of bringing promising research results, i.e. experimental malaria vaccines,

via limited industrial production to clinical evaluation in European volunteers and subsequently to clinical evaluation in developing countries in close collaboration with trials networks in malaria endemic areas.

In a joint effort announced in June 2001, EMVI has joined forces with the Malaria Vaccine Initiative (MVI) and USAID's Malaria Vaccine Development Program (USAIDMVDP) via a memorandum of understanding, in order to plan how to break through technical and financial barriers to vaccine development. They will also share information useful for the design of clinical trials and malaria vaccine development. A memorandum of intent has since been signed with WHO.

Foundation for Innovative New Diagnostics (FIND)

The Foundation for Innovative New Diagnostics (FIND) was launched on 22 May 2003 at the World Health Assembly in Geneva. This is a new, independent, non-profit foundation based in Geneva, which will work in close collaboration with WHO, the Special Programme for Research and Training in Tropical Diseases (TDR), academia, the diagnostics industry and other organizations. FIND is building on the success of a former TDR programme, the tuberculosis diagnostics initiative (see TBDI profile at www.ippph.org - Partnerships Database). With additional funding from the Bill & Melinda Gates Foundation, FIND will be able quickly to turn methods into products, untested products into fully evaluated products, and promising tests into tools with demonstrated impact and feasibility. FIND will apply the latest biotechnology innovations to develop and validate high-quality, yet affordable diagnostic tests, through the R&D pipeline, for diseases of the developing world. Ultimately, FIND aims to create a model for public action that resolves the current failure of market forces. The Gates Foundation has committed up to US$30 million over the next five years to the initiative. FIND will focus initially on TB diagnostics, in order to replace the current cumbersome sputum test for TB with a faster, more practical test to detect the disease, including drug resistant forms, and eventually move onto other infectious diseases.

Global Alliance for TB Drug Development (TB Alliance)

The Global Alliance for TB Drug Development is an international PPP accelerating the discovery and development of faster-acting and affordable drugs to fight tuberculosis. The TB Alliance builds and manages a portfolio of promising compounds with partners worldwide and invests in platform technologies that improve the environment for TB drug development. By providing staged funding, expert scientific and management guidance, and clear pre-defined milestones, the TB Alliance can ensure the rapid development of compounds. The TB Alliance pursues intellectual property rights to ensure that new drugs are affordable to and adopted by those most in need. The promise of TB control efforts will only be met fully when health-care workers are given the best tools that modern science can deliver.

Global Microbicide Project (GMP)

In 2000, CONRAD established the GMP to help develop new microbicidal agents that specifically address the needs and perspectives of women. The main objective of this project is to develop vaginal methods that would protect women against sexually transmitted infections (STIs), including HIV/AIDS. The GMP can provide funds for both pilot and major projects. Although there is no requirement for cost sharing by an industrial partner, it is strongly encouraged. At present, GMP funding comes solely from the Bill & Melinda Gates Foundation in the form of a US$25 million grant to expedite microbicide development.

Human Hookworm Vaccine Initiative (HHVI)

The Albert B. Sabin Vaccine Institute (SVI) is a United States non-profit educational and research organization dedicated to saving lives by stimulating the development of new vaccines, and increasing domestic and global immunization rates. Its programmes advance development of new vaccines and improved ways to produce and administer them. Founded in 1993, SVI is committed to continuing the work of polio vaccine developer Dr Albert Sabin, who envisioned the enormous potential of vaccines to prevent deadly diseases. The Institute currently operates from three sites: the national headquarters in New Canaan, Connecticut; the international programmes/public affairs office in Washington DC; and the HHVI headquarters in

Rockville, Maryland. The Institute is developing a vaccine to prevent an infection that afflicts almost 1 billion individuals, and is the leading cause of anaemia and malnutrition in the developing world. The HHVI, with the generous assistance of the Bill & Melinda Gates Foundation, sponsors vaccine research and development, under an US$18 million commitment started in April 2000. Research is conducted by vaccinologist, Dr Peter Hotez, a Senior Fellow at the Sabin Institute and the Professor and Chair of the Department of Microbiology and Tropical Medicine at The George Washington University. The research laboratories are located at The George Washington University Medical Center. Other aspects of vaccine development are being outsourced to several academic and industrial organizations.

Institute for OneWorld Health (IOWH)

The Institute for OneWorld Health (IOWH) is a tax-exempt non-profit pharmaceutical company launched in 2000 and based in San Francisco, California. Its mission is to develop safe, effective and affordable new medicines for diseases affecting people in the developing world, for which therapies either do not exist or are inadequate. Staffed with pharmaceutical scientists with international drug development and regulatory expertise, IOWH identifies promising drug and vaccine candidates and executes preclinical development, with the goal of regulatory approval of therapies in the most affected countries. Throughout the development process, from discovery to clinical trial to regulatory approval and manufacturing, IOWH collaborates closely with a range of global health players, including WHO, major research universities, the Walter Reed Army Institute of Research, the National Institutes of Health and the various pharmaceutical companies. IOWH seeks public sector funds to pursue projects that could be promising for the developing world but which may not attract private investment funds. Once new drugs are approved for use by regulatory agencies, manufacturing and distribution are outsourced to quality corporations in the developing world to maintain IOWH's focus on drug development. It is anticipated that differential pricing will be applied to all of IOWH's drugs, to ensure affordability.

International AIDS Vaccine Initiative (IAVI)

IAVI is a United States tax-exempt, not-for-profit scientific organization established in 1996 to ensure the development of safe, effective and accessible preventative HIV vaccines for use throughout the world. IAVI is a collaborating centre of UNAIDS and works with both public and private sector organizations in pursuing its mission. IAVI's work focuses on four areas: creating global demand for AIDS vaccines through advocacy and education; accelerating scientific progress; encouraging industrial involvement in AIDS vaccine development; and assuring global access. IAVI funds and sponsors fast-tracked product development and clinical testing of promising AIDS vaccine candidates developed for the countries most affected by the disease. IAVI's major financial supporters include the Bill & Melinda Gates Foundation; the Rockefeller, Sloan and Starr foundations; the World Bank; Becton, Dickinson & Co.; the Canadian International Development Agency (CIDA); and the governments of the Netherlands, United Kingdom, United States, Ireland, Denmark, Norway and Sweden. IAVI has now secured commitments totalling US$310 million, towards a goal of US$655 million by 2008.

International Partnership for Microbicides (IPM)

The International Partnership for Microbicides (IPM) is a PPP formed in 2002 to accelerate the discovery, development and accessibility of microbicides to prevent transmission of HIV, especially among women in low-resource settings. Through review and prioritization, the IPM provides resources and expertise for targeted, milestone-driven projects in its core areas of product development and access. IPM is supporting development initiatives across the microbicide pipeline, especially agents with new modes of action, and investing in efforts to provide the field with shared technologies (e.g., novel long-acting formulations) and resources (e.g., expanded clinical research capacity.) IPM is also identifying and supporting policy and programmatic initiatives that will facilitate rapid approval and introduction once effectiveness has been demonstrated; initial work is in the areas of financing, regulatory affairs and country preparedness. Finally, IPM works to raise awareness and resources for microbicide development. A recent analysis conducted by experts at the London School of Hygiene and Tropical Medi-

cine, based on real data from 73 low-income countries, concluded that a 60% efficacious microbicide, used by 20% of people easily reached through existing health services, in one-half of the occasions when condoms are not used, would avert 2.5 million new infections over three years in women, children and men.

Malaria Vaccine Initiative (MVI)

Based in Rockville, Maryland and Seattle, Washington, MVI was started with seed funding of US$50 million from the Bill & Melinda Gates Foundation in June 1999. MVI is administered by Program for Appropriate Technology in Health (PATH), aUnited States tax-exempt, not-for-profit organization. MVI's mission is to accelerate the development of malaria vaccines and ensure their availability in the developing world. Funds are directed to vaccine development partnerships with industry, biotechnology firms, government agencies and academia. Each project may support process development, production and/or clinical trials in malaria-endemic regions. Technical advisory groups and PATH's board guide MVI. Partners include malaria experts around the world, government agencies, academia, public and private research institutions, and vaccine producers. Business development, communication, and policy activities support the vaccine development partnerships and seek to improve the environment for malaria vaccine development and introduction.

Medicines for Malaria Venture (MMV)

The Medicines for Malaria Venture (MMV) was created in 1999 as a Geneva-based not-for-profit organization under Swiss law, to discover, develop and deliver new antimalarial drugs that are effective and affordable. MMV receives funding and support from the following organizations: the Bill & Melinda Gates Foundation; ExxonMobil Corporation; Global Forum for Health Research; International Federation of Pharmaceutical Manufacturers Associations (IFPMA); WHO; the Rockefeller Foundation; the World Bank; Roll Back Malaria global partnership; TDR; the United Kingdom's Department for International Development (DFID), Swiss Agency for Development and Cooperation, the Netherlands Minister for Development Cooperation and the Wellcome Trust. MMV also receives contributions in-kind, such as management expertise, access to chemical libraries, high throughput screening and data handling from pharmaceutical companies, biotech firms, universities and research institutes. MMV's goal is to identify one new drug every five years with the first one by 2010. In order to reach its goal, MMV has built up the largest antimalarial drug research and development portfolio in history, which currently consists of 21 projects in different developmental stages. Within its 11 discovery and 10 development projects, MMV has eight completely new therapeutic targets in the pipeline. The clinical development projects are gaining momentum and several of preclinical projects are set to move into clinical studies in 2004. Its desired full operating annual budget is US$30 million.

Microbicides Development Programme (MDP)

MDP is a partnership to accelerate the evaluation and development of vaginal microbicides for the prevention of HIV transmission. Established in 2001, the programme is funded by DFID and administered by the Medical Research Council Clinical Trials Unit and Imperial College London. The central goal of the partnership is to complete a phase III effectiveness trial of candidate microbicides in multiple sites in sub-Saharan Africa. Currently, feasibility studies to estimate incidence and assess condom usage are currently being conducted in Tanzania, Zambia, Uganda and three sites in South Africa. Furthermore, MDP aims to develop new products to enter safety studies in the United Kingdom and Africa; to conduct social science research into the acceptability and possible barriers concerning the uptake of the products; and to facilitate marketing and access to a successful microbicide.

Pediatric Dengue Vaccine Initiative (PDVI)

The Pediatric Dengue Vaccine Initiative (PDVI) represents a public-private effort to raise awareness of the need for and accelerate the development of a dengue vaccine that is appropriate, safe and accessible to poor children in endemic countries. Dengue is a mosquito-borne viral disease that affects tropical regions around the world. Every year, in addition to tens of millions of cases of severe dengue fever, an average of 500,000 people, mostly children, are hospitalized with dengue haemorrhagic fever with high case fatality rates. No specific, effective treatment is available and vector-con-

trol strategies have been insufficient to counter the pandemic. This led the Rockefeller Foundation and the International Vaccine Institute to convene a meeting in 2001 to focus on the challenges and opportunities for the development of a paediatric dengue vaccine. The meeting, and related working-group processes, have energized the field and built unprecedented momentum to bring about a coordinated global effort. This coincides with a 2002 resolution by the World Health Assembly that stresses the negative impact of dengue on health and development.

Pneumococcal Vaccines Accelerated Development and Introduction Plan (PneumoADIP)

The Pneumococcal Vaccines Accelerated Development and Introduction Plan, PneumoADIP, is an independent group located at the Johns Hopkins School of Public Health and funded by GAVI. Its mission is to improve child health by accelerating the evaluation of and access to new life-saving pneumococcal vaccines for the world's poorest children. PneumoADIP aims to shorten the time lag between the use of a new vaccine in rich countries and its use in poor countries by working to achieve a sustainable, affordable supply of quality vaccines by reducing the uncertainty of demand for the vaccine in the world's poorest countries.

Rotavirus Vaccine Programme (RotaADIP)

In 2003, with funding from GAVI and the Vaccine Fund, PATH established the Rotavirus Vaccine Programme. RotaADIP is a limited liability company of PATH. Its mission is to reduce child morbidity and mortality from diarrhoeal disease by accelerating the availability of rotavirus vaccines appropriate for use in developing countries.

South African AIDS Vaccine Initiative (SAAVI)

In 1999, it was decided that South Africa should develop its own HIV/AIDS vaccine. This led to the formation of the South African AIDS Vaccine Initiative (SAAVI), a national body coordinating the research, development and testing of HIV/AIDS vaccines in South Africa with the aim of producing an affordable, effective and locally relevant preventative HIV/AIDS vaccine. SAAVI receives funding from the South African government, Eskom and international organizations. SAAVI is based at the South African Medical Research Council.

APPENDIX D

Examples of PD PPPs based on specific candidate products

Infectious Disease Research Institute (IDRI)

A joint industry research programme of the IDRI, which is a United States, tax-exempt, not-for-profit scientific organization supported by public funds. In 1994 IDRI established a collaborative partnership with Corixa Corporation, an R&D-based biotechnology and vaccine company. The goal of the partnership is to optimize the development of vaccines, therapeutics and diagnostics against leishmaniasis and diagnostics against diseases of developing countries. In March 2000, IDRI received a US$15 million grant from the Bill & Melinda Gates Foundation to fund their ongoing effort to develop a vaccine to prevent and treat leishmaniasis. This programme is being carried out in collaboration with Corixa, and supported in part by funding from the National Institutes of Health . In January 2003, IDRI and Corixa announced initiation of a US-based phase I clinical trial of a candidate vaccine against leishmaniasis.

Lapdap Antimalarial Product Development (LAPDAP)

A joint research agreement was signed in March 2001 between WHO through its United Nations Development Programme (UNDP)/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR) and GlaxoSmithKline to develop a new effective oral treatment for uncomplicated malaria, primarily for use in sub-Saharan Africa, at preferential prices for public health programmes. The aim is to develop chlorproguanil-dapsone (Lapdap™) for regulatory submission as a safe alternative to chloroquine and sulfadoxine-pyrimenthamine (SP) for treatment of malaria caused by the *Plasmodia falciparum* malaria parasite in Africa. To date, clinical phase III trials on LAPDAP have been conducted in Gabon, Kenya, Malawi, Nigeria and Tanzania. Funding is provided by WHO/TDR, GSK and DFID. The file was submitted to the British Medicines and Healthcare Products Regulatory Agency (MHRA) in November 2002. A marketing authorization was issued by the MHRA in July 2003. The dossier has been submitted to many African national authorities, and marketing approval has been granted in some coun-

tries. Lapdap™ has been launched commercially in several countries.

Gates Foundation/University of North Carolina Partnership for the Development of New Drugs (GFUNC)

GFUNC was established in 2000 with a US$15.1 million five-year grant. The overall goal of this partnership is to develop potent, safe, orally active and economical new drugs to treat African trypanosomiasis and leishmaniasis. This partnership has brought together experts, researchers and clinicians from around the world, with academia, governments international organizations, private institutions and industry all involved in the field of clinical development and drug discovery therapies to fight these diseases that are killing and infecting millions of people in African-endemic countries.

Meningitis Vaccine Project at WHO/PATH (MVP)

MVP is a partnership between WHO and the Program for Appropriate Technology in Health (PATH) created with the technical advice of the United States' Centers for Disease Control and Prevention, to eliminate epidemic meningitis in sub-Saharan Africa. The project aims to develop a viable serogroup A meningococcal conjugate vaccine within five years by leveraging the strengths of the public and private sectors to commission the development of a vaccine that would not otherwise be commercially feasible. The project is a ten-year programme, with initial funding of US$70 million from the Bill & Melinda Gates Foundation in May 2001, which will ensure the delivery of this vaccine through mass and routine immunization programmes for children and adults in affected countries. Key partners include vaccine companies and international and national groups working to prevent and respond to meningococcal meningitis epidemics in Africa.

For other examples, please see the Partnerships Database at www.ippph.org.

ANNEX 3B

Background on the concept of the workshop

Proposed workshop: Combating diseases associated with poverty: Financing strategies for product development and the potential role of public-private partnerships

Summary

The Initiative on Public Private-Partnerships for Health,[1] a component of the Global Forum for Health Research, is organizing a workshop to explore the potential contributions of public-private partnerships (PPPs) for product development (PD) to combating diseases associated with poverty. The meeting will consider in particular the roles, relationships, activities, 'added-value' and financing needs of those PD PPPs specifically utilizing a 'portfolio management approach'. The workshop will also cover the context in which such ventures operate, namely between more fundamental research and new product utilization, and the activities by various other players which are necessary to support their ultimate success.[2]

Background

A wide range of organizations in both public and private sectors have an interest in contributing to the reduction of diseases associated with poverty in developing countries, which is a major component of the Millennium Development Goals (MDGs). Obviously, the responsibility to organize the delivery of health services falls ultimately to the respective governments, but in developing and supplying health products needed in poorer countries, many other players are involved. These organizations include funders such as multilateral and bilateral aid agencies, private philanthropic foundations, scientific agencies and organizations (including pharmaceutical companies), and others that can assist implementation, such as health services nongovernmental organizations (NGOs).

While some tools exist for combating many diseases and other health problems associated with poverty, better tools (vaccines, drugs, diagnostics, topical microbicides, contraceptives, etc.) are needed for almost all and in particular HIV/AIDS, malaria and tuberculosis. In some cases there is little prospect of meeting the MDGs without new or better products. Developing and putting into use these new or improved tools entails a complex, multi-step process of basic and targeted research, product development including clinical efficacy trials in disease-endemic countries, manufacturing process development, regulation, pilot/demonstration projects and procurement for routine utilization. In this 'chain', many actors and funders can play a role. However, for products to combat health problems that predominantly or exclusively affect poor people around the world, there is little motivation for commercial companies independently to apply their expertise in product development and manufacture. The risks and costs, including opportunity costs, outweigh the low potential future revenues. There has been much discussion over the last few years of so-called 'push' interventions (to reduce the costs and risks to industry) and 'pull' interventions (to ensure a greater market), but relatively little substantive action has emerged in the public policy arena. Welcome exceptions to this generalization include some new World Bank financing mechanisms, the Vaccine Fund (VF), associated with the Global Alliance for Vaccines and Immunization (GAVI), and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) which give some hope of procurement and application of new and better products. The latter two however both need more resources to meet demand from the poorer countries.

[1] The Initiative on Public-Private Partnerships for Health (IPPPH) was established in 2000, under the Geneva-based Global Forum for Health Research, to monitor, analyze and support ventures in public-private collaboration to reduce global health inequities associated with poverty.

[2] This proposal was initially distributed in the latter half of 2003.

Over the last decade, and particularly in the last three to four years, there has, however, been significant growth in the number of groups attempting to develop tools to combat the diseases and other health problems associated with poverty, through so-called 'public-private partnerships' engaging commercial pharmaceutical companies.

This phenomenon arises from increasing recognition that the expertise to turn scientific research into useful health products (drugs, vaccines, diagnostics, contraceptives, microbicides, impregnated bed-nets, etc.) resides overwhelmingly in commercial, private sector industry, but that products to combat the health problems that predominantly afflict the poor are not commercially attractive, compared to those that would be used by more affluent populations.

PPPs are *inter alia* a way of engaging commercial expertise through lowering the risk and costs to industry. However, in addition to paid contributions, the private sector often contributes additional in-kind resources (see IPPPH, 2002).[1] Hence, the total cost may be less than 'full-price' contracting for all activities, even assuming that companies would divert human and other resources even if cash only for R&D was on offer, without other factors that PPPs bring to the collaboration.

Public-private partnerships do not simply pass on resources to industry but also become engaged in orchestrating the linkages necessary to channel basic research concepts through to improved health for the poor. In this role they can shorten the time required to apply investments in basic research to health. They also engage in advocacy to raise awareness of health needs among poor populations and in so doing, mobilize moral support and new resources to this goal.

These PPPs usually attempt to keep a range of products at different stages of development moving down the 'development' pipeline'. This so-called 'portfolio management approach' (PMA) is adapted from business methods in the pharmaceutical industry. It is derived to maximize statistically the likelihood of ultimate success, given probable candidate product failures that are predictable, statistically if not individually. The PMA has cross-project learning synergies and particular implications for financing requirements. The financing needs of portfolio management are fundamentally different to the project-by-project funding approach usually practised for more basic research.

A limited range of funders, including bilateral development agencies and foundations (such as the Bill & Melinda Gates Foundation and the Rockefeller Foundation), has invested significantly in product development PPPs in the health sector – believing they offer a new approach. Other potential funders have chosen not to make such a commitment, at least at this point. It is not clear whether they have just delayed considering such funding or have so far unanswered questions regarding the role that PD PPPs can play, the rationale for them or their operations. Other funders may indeed play a role mostly in financing research that feed the PPP pipelines or financing procurement, and thus ensuring the ultimate utilization of their new products. In all cases there would be considerable benefit in better understanding the potential roles and links necessary to ensure an efficient transfer of promising candidate concepts/products down the development chain, preferably with some assurance of mechanisms and funding for eventual uptake

A number of PD PPPs have now accumulated a few years' experience. It is, therefore, a reasonable time for an interim assessment of the approach, its costs, possible alternatives and overall lessons learned to date. Options for further innovative financing need to be considered in addition to the traditional sources. Additional topics that also need addressing are:

- What else needs to be in place for PD PPPs as currently conceived to do their task effectively? How can links in the chain from research to use be optimized?
- What tools are available to measure progress in targeted research and product development?
- What are the benefits of assured financing for uptake to interest in product development?

The workshop proposed by IPPPH is an opportunity to deepen and broaden understanding of this fundamentally new approach and to assess its prospects, costs and implications. It will necessarily include representatives of selected PD PPPs to explain their approaches. However, it is not intended to be a means through

[1] Kettler H, White K. *Valuing Industry Contributions to Public-Private Partnerships for Health Product Development*. Geneva: IPPPH, 2003.

which individual organizations will pursue their own particular fund-raising objectives.

The workshop is relevant to all organizations desiring to contribute to reducing the global burden of disease associated with poverty, in that better tools to combat such health problems are needed to assist in achieving most of the MDGs. Organizations that should be represented include:

- Bilateral and multilateral aid agencies whether funding R&D for health products or health services delivery
- Philanthropic foundations supporting basic research, product development or disease control programmes
- Technical agencies funding research, product development and/or public health programmes
- Health policy-makers from developing countries
- Pharmaceutical companies and PPPs engaged in product development.

The option is available for funders to convene a satellite meeting to consider separately their responses to the recent creation of a number of PPPs (including especially those involved in product development) and the issues raised in the workshop.

The desired outcomes of the IPPPH workshop are:

- A broader and deeper understanding among participants of the mode of operations of PPPs for the development of products to combat developing countries' neglected health problems and their potential roles
- Achievement of consensus (to the extent possible) on actions needed to maximize their potential to contribute to the alleviation of diseases associated with poverty
- Identification of questions or issues needing further clarification
- Establishment of a Follow-up Monitoring Group to assess the impact of the workshop and propose desirable next steps.

Draft objectives, proposed outputs, proposed participants and a preliminary agenda are provided in the following pages and comments on these would be welcomed.

The objectives of the workshop

- To provide background on the emergence and operations of PD PPPs for 'neglected' health problems:
  - — How did we derive the PD PPP model for development of pharmaceuticals needed to combat diseases associated with poverty?
  - — How and why did the portfolio management approach evolve in industry to maximize statistically chances of success?
  - — Why is it appropriate to not-for-profit PD PPPs?
  - — How is it different to traditional funding for research projects, e.g. in academia?
- To consider how PD PPPs and other players operate and interact in the 'chain' by which scientific knowledge is developed and applied for global health:
  - — How can the transition at the research/product concept to product development interface be best expedited, specifically in cases where candidate products have low commercial attractiveness?
  - — What else needs to be in place for PD PPPs to do their tasks effectively?
  - — Beyond portfolio management, what value do PD PPPs add along the product development chain?
  - — What 'metrics' can be used for measuring progress in research and product development?
  - — How can we best anticipate and ensure the rapid uptake of suitable new products to routine use?
- To assess if innovative financing options for 'neglected products' exist
- To assess the current financial situation of PD PPPs that use the PMA, given their need for a 'critical mass' of products in the pipeline for best economies of scale, likelihood of success and cross-project learning
- To reassess original predictions of financial requirements of PD PPPs and predict their future financial needs
- To evaluate what are the relative costs of investing in alternative approaches to ensuring the development of products needed to combat diseases associated with poverty (i.e. other than the PD PPPs using the PMA)
- To consider what PPPs, various funders, private

sector organizations and others should do based on information presented and discussions at the workshop.

Outputs of the workshop and follow-up process

- Establishment of a small Follow-up Monitoring Group (of about six persons drawn from constituencies represented at the meeting) to assess actions taken as a result of conclusions reached at the workshop and periodically to guide the IPPPH Secretariat on desirable next steps
- A report of the workshop presentations and discussions, including background papers, disseminated widely within three months of the workshop
- Approximately 12 months after the workshop, an external evaluation of actions probably resulting from the workshop and a summary report on desirable next steps based on the external evaluation and consultations with the Follow-up Monitoring Group.

Potential participants

- Funders of research, product development and public health programmes (i.e. disease control and health services delivery):
  - — Foundations
  - — Bilateral development agencies
  - — Government research funding agencies
  - — Multilateral agencies
  - — Developing country governments
- Representatives of pharmaceutical and 'biotech' companies and venture capital investors
- Representatives of existing 'partnerships' for development of products needed primarily in developing countries: from among GATBDD, IAVI, IPM, MMV, MVI, Institute for OneWorld Health, Aeras, FIND and DNDi/MSF, possibly others
- Selected representatives from low-income countries, in which the target health problems are endemic
- Other selected participants.

ANNEX 4

Purpose of the meeting: Opening Remarks

Roy Widdus (Initiative on Public-Private Partnerships for Health, Geneva, Switzerland)

- There has been a dramatic increase in attention to 'neglected diseases' in the last five years:
  - — This has occurred on many varied fronts rather than being the result of a systematic effort
  - — Health in developing countries has gone up the political agenda, as symbolized by the widely accepted Millennium Development Goals (MDGs) and the creation of Global Fund (GFATM)
  - — 50% of the MDGs are related to health directly or indirectly (see Annex 5).
- Prospects for achieving the 2015 targets for the MDGs without new tools to combat diseases associated with poverty are fairly bleak:
  - — Most resources and discussion about achieving the MDGs focus on applying existing tools
  - — Available tools must be applied, but for the major diseases the array of existing tools is inadequate and, for the most neglected diseases, the situation is even worse.
- This meeting pulls together most of the key actors relevant to combating neglected diseases more effectively through improving the tools available:
  - — It is, as far as we know, the first time that such a stellar array of talent has been gathered in one place on the specific topic of product development for neglected diseases
  - — It can also be ***unique*** if we all take off our usual fundraising, donor or industry 'hats' and focus on the exchange of information
  - — This workshop is an exercise in melding different cultures and different ways of doing business (but we are not looking for 'a one-size fits all' model).

This is a special opportunity to consider collectively three topics that are important to future progress:

1. How can we most usefully define and conceptualize the 'field'?
   - Public health history has repeatedly taught the lesson that the uptake of appropriate, new products does not occur automatically.
     - — Have we learned this lesson? Gargee Ghosh's paper (*see* Background paper 9i.) suggests some hope in the area of vaccines but efforts in planning new drug introduction are rare
   - If the ultimate goal of product development is public health impact we must identify and ***someone*** must address potential delays in 'access'
   - Many of the PPPs at the workshop are committed to work on 'access' but perhaps we should also be looking for other organizations to play a bigger role in ensuring access – particularly as it is usually considered a public sector responsibility
   - If the goal is the highest public health return on investment (PH-ROI), then we must create a commonly agreed and used way of expressing PH-ROI that expresses potential public health benefit incorporating as well the cost to develop and deliver the products.

Correctly conceptualizing the problem – as being the pursuit of public health impact – is essential to solving it; otherwise we just shift the bottleneck, simply creating a bigger backlog of underused products.

2. How to improve understanding, communication and coordination among implementers and funders?
   - With products to combat diseases that are not commercially attractive, we have a multitude of players engaged at many different stages. To be successful in a reasonable time we must ensure that they work more in unison:

  - — Along the research-development-access continuum
  - — Across those engaged in similar activities
  - — Among disease-specific and broader health system activities.
- Shared terminology is desirable but at least understanding each other's usage is a start
- We learnt in the preparations for the meeting that individual PPPs see their activities as unique and often take a while to get used to ways of describing what they do that are not the ones they are familiar with
- Better communication and 'hand-offs' will be an ongoing challenge, so how do we achieve and sustain coordination on these over time?

3. How to make future decisions based on better information?

- Better estimates of the financing needed are part of this process
- What are the other important things that should be tracked?
- What are the important things to analyse further?
- How do we define the trade-offs across all the possible ways to invest available resources?
- How do 'we' get these things done to high quality in an impartial manner?

There are many discrete issues that will need to be considered before we can get to consensus on these three overarching questions.

The issues can be grouped as those relating to the broader field and those that relate to the individual product development partnership.

We have laid some issues out in the listing that is an attachment in the printed copy of these opening remarks and the "Questions by Sessions" (*see* Annex 7).

This meeting will hopefully start consideration of these issues – but we should be realistic. Above all there is no sense among the organizers that we can prescribe a perfect model.

It is perhaps more important to decide how to continue the information exchange and analysis than to believe that all questions can be decided at this meeting. So we have three key challenges to keep in mind for the closing session:

- How do we define and conceptualize the field? As ending at new product licensure or at public health impact? And if 'access' is included, what is an appropriate role for PD PPPs in ensuring we get the fullest PH-ROI in developing new tools for preventing, diagnosing or treating neglected diseases (PH ROI is the surrogate for the 'pull' of a market)?
- How do we improve communication, exchange of experience and coordination?
- What needs tracking and analysing?

Attachment
Some of the issues identified in preparations for the workshop
At the level of the overall field of products to combat 'neglected diseases'

- How should the field be conceptualized? The analytical frame can be limited to product development *per se*. However, highlighting what is necessary to achieve 'access' enables parallel attention to problems that may otherwise create bottlenecks and seriously impede achieving potential public health impact. This attention may best be from others with more direct 'downstream' responsibilities, rather than the PD PPPs themselves. But it must occur.
- Can and should the field be 'managed' systematically? Gaps in needed product development activities and overlapping PD PPP missions are a cause for concern.
- If 'management of the field' is to be attempted should this be by funders or by coordination among implementers, e.g., PD PPPs, or a combination of both?
- How can better coordination among funders and implementers be achieved:
  - — Along the research-development-access continuum
  - — Across funders or implementers engaged at particular steps along the continuum
  - — Among disease-specific and overall health system players?
- How can funders obtain impartial advice when faced with proposals for financing expensive investments (e.g., major clinical trials) on which proponents disagree widely (e.g., HIV/AIDS vaccines, microbicides)?

- Given the potential value to many actors of methods to compare the potential public health benefits of different anticipated products, and the investment necessary to achieve them, how best to support their development and impartial application?

At the level of individual PD PPPs

Disease/product-focus selection fundamentally determines scientific challenge and the context for addressing 'access'. Thus, this choice influences the probability of success, likely necessary investment, and also potential public health impact. Hence at the level of individual PD PPPs the questions are:

- Does there exist a situation analysis of barriers to product development and access that is comprehensive (along the research-development-access continuum) of high quality, and broadly agreed, identifying the 'needs' for this disease/product focus?
- How well does the 'niche' adopted by the PD PPP match the 'needs' identified in the situation analysis?
- How realistic is the breadth and challenge of the disease/product focus in relation to the proposed operational of style and size. Is it likely to reach a critical mass necessary for efficient operations?
- How well do the choices regarding independent or hosted status, sector roles and collaborators, and operational style (management oversight, portfolio development and management) recruit necessary contributions from potential partners, including those from business/'pharma' (expertise and in-kind contributions for product development) and the public sector (expedited regulatory processes, timely public health guidelines, efficient distribution system)?
- Does the PD PPP have a clear concept of *its* 'added value' and is it measuring/reporting this, as well as the progress of the science?
- Does it have evidence of in-kind contributions (and their value) to show the added value of a PPP approach for its disease/product focus?
- Is there evidence of rigorous application of 'best practices' in portfolio management and accessing the highest-quality scientific advice?

ANNEX 5

UN Millennium Development Goals

THE GOALS	IMPLEMENTATION
1 Eradicate extreme poverty and hunger	■ Reduce by half the proportion of people living on less than a dollar a day ■ Reduce by half the proportion of people who suffer from hunger
2 Achieve universal primary education	■ Ensure that all boys and girls complete a full course of primary schooling
3 Promote gender equality and empower women	■ Eliminate gender disparity in primary and secondary education preferably by 2005, and at all levels by 2015
4 Reduce child mortality	■ Reduce by two thirds the mortality rate among children under five
5 Improve maternal health	■ Reduce by three quarters the maternal mortality ratio
6 Combat HIV/AIDS, malaria and other diseases	■ Halt and begin to reverse the spread of HIV/AIDS ■ Halt and begin to reverse the incidence of malaria and other major diseases
7 Ensure environmental sustainability	■ Integrate the principles of sustainable development into country policies and programmes; reverse loss of environmental resources ■ Reduce by half the proportion of people without sustainable access to safe drinking water ■ Achieve significant improvement in lives of at least 100 million slum dwellers, by 2020
8 Develop a global partnership for development	■ Develop further an open trading and financial system that is rule-based, predictable and non-discriminatory. Includes a commitment to good governance, development and poverty reduction – nationally and internationally ■ Address the least developed countries' special needs. This includes tariff- and quota-free access for their exports; enhanced debt relief for heavily indebted poor countries; cancellation of official bilateral debt; and more generous official development assistance for countries committed to poverty reduction ■ Address the special needs of landlocked and small island developing States ■ Deal comprehensively with developing countries' debt problems through national and international measures to make debt sustainable in the long term ■ In cooperation with the developing countries, develop decent and productive work for youth ■ In cooperation with pharmaceutical companies, provide access to affordable essential drugs in developing countries ■ In cooperation with the private sector, make available the benefits of new technologies – especially information and communications technologies

ANNEX 6

Keynote address

Linking private sector expertise in product development with public sector goals to combat global health problems

Gail H. Cassell, Ph.D. (Vice President for Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company, Indianapolis, IN, USA)

A summary prepared by the Secretariat of the Initiative on Public-Private Partnerships for Health

In reality, bringing a new drug from concept to the patient is exceedingly complex,[1] but the multitude of steps is necessary because of attrition among candidates, and the requirements of assuring safety for consumers.

Industry invests in iterative chemical synthesis, target selection, high throughput screening, animal testing, pharmacokinetic analysis, toxicology and optimization of efficacy/pharmacokinetics. It also invests significantly in developing production and quality assurance methods, as well as clinical studies (Phase I, II, and III), application for regulatory approval (for marketing). Post registration Phase IV studies also are often conducted in addition to surveillance of adverse reactions.

At any particular point in time a range of candidate products will be at various stages in the overall pipeline for each major product class. As of the London meeting antibacterials in clinical development, among various companies comprised (at least) 11 candidates in Phase I (or unknown clinical phase), seven candidates in Phase II, and nine candidates in Phase III. In the preceding two years, seven products in this category had been launched. The pattern was similar for anti-virals, however, with fewer new products launched. For anti-malarials, even including products being co-developed with one of the product development partnerships the number of candidates was significantly fewer. Anti-tuberculosis candidate were somewhat more numerous, but mostly at the pre-clinical stages.

Statistically observed attrition rates and industry standards for the duration of pipeline steps can be used, with estimated costs, to suggest the desired pipeline composition and its cost implications. An example for new anti-malarials was presented.

The pharmaceutical industry in general however is observing lower success rates in development of new molecular entities (NMEs) over at least the last decade. The Economist magazine had noted an overall fall in NMEs approved annually between 1991 and 2003 by approximately 50% despite a two-fold rise in global research and development expenditures.[2] Lilly itself had managed to maintain research productivity but the situation was a challenge.

Despite the general industry desire to increase productivity, and to also see products emerge to meet the needs of the poor, no part of the product development chain was dispensable, even in 'public health emergencies'. Lowering safety standards in development of certain classes of new product (such as those for developing countries) would be at odds with basic human rights. The quality issue for existing products used in many developing countries was however a cause for serious concern since a high proportion of locally manufactured and imported products failed to meet required standards.

Developing drugs to confront diseases associated with poverty represented a challenge to all the parties wishing this to occur as no single player has the resources or incentives to manage the entire process. Not surprisingly (since markets were unattractive) there was a disconnect between development of NMEs targeting diseases associated with poverty and the health burdens these diseases represented worldwide. Even among the diseases typically associated with poverty, some (such as Trypanosomiasis, Chagas Disease, Schis-

[1] Nwaka S, Ridley R. 2004. Virtual drug discovery and development for neglected diseases through public-private partnerships. *Nature Reviews Drug Discovery*, 2:919–928.

[2] *The Economist Technology Quarterly*, March 2004, pp.38.

tosomiasis, Leishmaniasis, Lymphatic filariasis, and others) showed disproportionate impact in high mortality developing countries.

Development of new and improved 'tools' to combat diseases associated with poverty represented a situation where collaboration was the only rational approach:

- Public authorities and/or philanthropic groups may have the resources but they lack the infrastructure to carry out the development process;
- Academic researchers may have promising biomedical leads but they lack the development testing and manufacturing expertise to bring drugs to patients; and
- Private drug companies may have the development, testing and manufacturing expertise but they lack the necessary financial incentives where the public health needs of the developing world are concerned.

Many new product development partnerships were showing promise in product development. These included the Global Alliance for Tuberculosis in Drug Development, on whose Board Dr Cassell served. Furthermore, other collaborations involving pharmaceutical companies were underway ramping up manufacturing capabilities, educating health care providers at the community level, providing products, ensuring their delivery and tracking outcomes. One collaboration in which Lilly itself was involved was the transfer of manufacturing technology for two drugs against multi-drug resistant tuberculosis (MDRTB) to low-cost producers in developing countries where MDRTB was an increasing problem.

Another approach to enabling public and private sectors to join forces for public health purposes was to expand the networks traditionally used to solve problems. Untapped pools of talent undoubtedly existed in less well-known academic institutions contract research laboratories, in advanced and even the least developed countries, in other fields related to biomedical research and among those retired. Lilly had fostered one such collaborative problem solving model using the Internet to reach further InnoCentive.[1] Over 150 scientific challenges had been posed via this system resulting in 50,000 respondents from over 100 countries. Awards to the best solution had been made in 46 cases (with full protection of the innovators intellectual property). This novel collaborative approach to problem solving had been utilized by a range of problem setting companies in pharmaceuticals, basic and special chemicals, petrochemicals, food flavours, fragrances, agribusiness, biotechnology and consumer products.

Dr Cassell viewed the future of public-private collaboration very optimistically:

- Public-Private Partnerships (PPPs) represent the most promising solution so far to the 'disconnect problem', between resources, goals and skills needed for development of new products to combat diseases associated with poverty;
- By infusing public and philanthropic money into the process, PPPs restore some of the financial incentives to private firms (corporate social responsibility should close the rest of the gap);
- PPPs also succeed by replicating the portfolio-management approach to traditional drug development, and targeting it on neglected diseases;
- PPPs 'translate' the work of basic academic research into serious drug candidates, and manage the development, testing and approval process;
- The dollars of well-intentioned government and donors will be used more effectively than in the past;
- We have learned not to neglect any part of the process – including the stages of drug development but also the "deployment" of new therapies;
- The bottom line is that the players each know their places: what they're good at and what they're not so good at;
- The challenge now is to figure out better ways to bring the best of the public and private sectors together and even enhance the current PPPs.

[1] InnoCentive website: www.innocentive.com

ANNEX 7

Questions by Sessions

Peter Hall

Overarching questions

- Overall, are the goals and objectives of existing PD PPPs based on meeting major public health needs and achieving access to products for the poor in developing countries? Are all major needs covered?
- How did founders and/or funders of particular PPPs determine the 'need' and the PD PPP's 'niche' to address that need? (Was there a broad consensus development process to get wide buy-in?)
- Are there overlapping PPP missions? Is this healthy competition or wasteful duplication?
- Are there public health needs that are not being addressed?
- Could/should a more systematic approach to identifying and addressing 'needs' (for improved disease control tools) be developed? If so, who should drive this process?
- Can a common terminology be developed to describe the strategic, operational and financial models of different PPPs?
- Can a methodology be developed to allow comparison of strategic approaches, operational mechanisms, financial needs and ability to meet public health needs between PPPs?
- If the ultimate goal of product development is public health benefit, how well are different PPPs doing in quantitatively estimating their likely public health impact (as opposed to the burden of disease they address)?
- What are the funding requirements to ensure that appropriate products for neglected diseases are developed and become accessible at an affordable cost to those that require them? How can we improve these estimates?

Hierarchy for individual PD PPPs

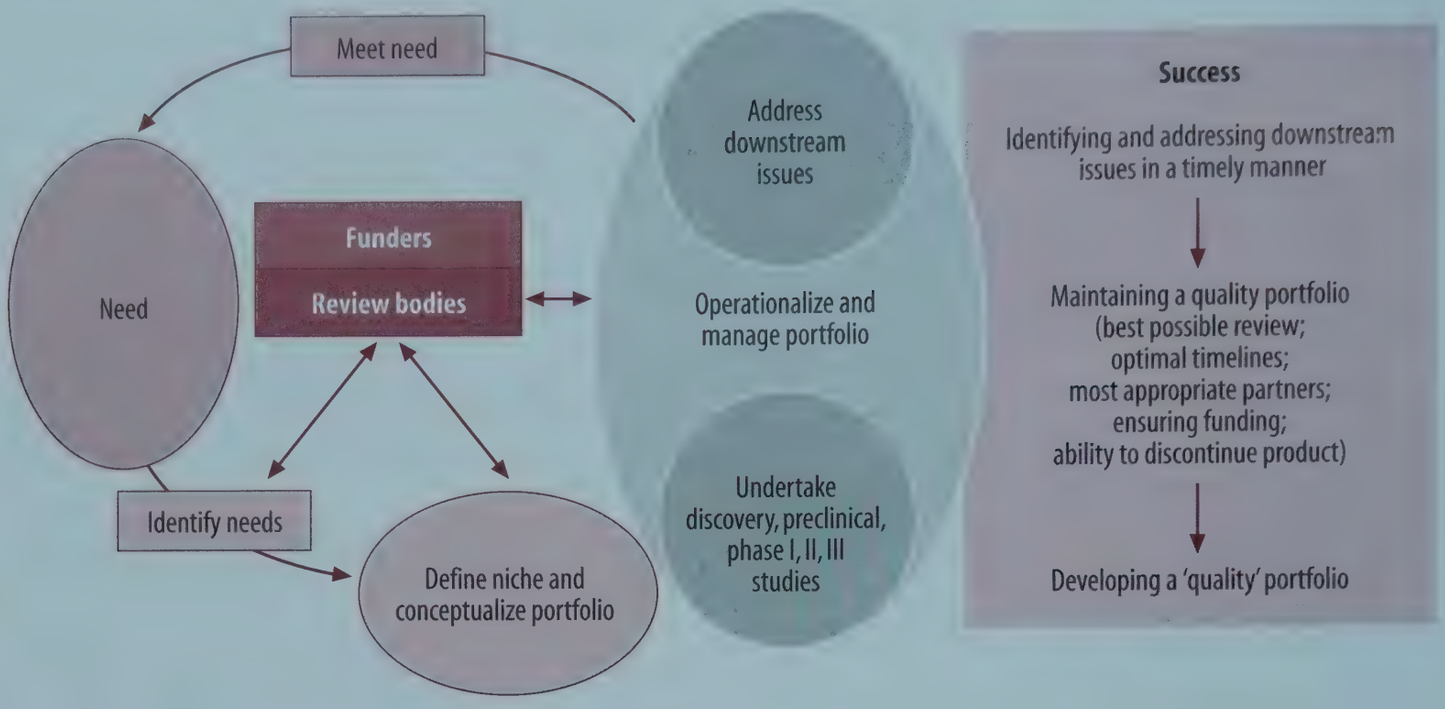
- How to identify need, define niche and conceptualize portfolio?
- How to operationalize and manage portfolio?
- How to link upstream/midstream/downstream issues?
- How to determine success?
- How to determine and meet financing needs?
- How to determine value for money?

See Figure 1 overleaf.

Session I. The rationale for PPPs: Determining need and niche

- How and why have existing PPPs been established?
- Before establishing a PPP, has there been a systematic analysis of: potential impact on burden of disease; the public health impact on specific countries or population groups; ongoing or planned development activities in the field; availability of expertise; and the potential value-added? Is this still needed in certain areas of activity?
- How have PPPs identified an appropriate niche? What is the product/disease focus?
- How have existing PD PPPs determined what is a reasonable scope?
- Where there has been a good review of need, has this been adequately related to ongoing activities being undertaken by others in order to identify niche?
- How has the objective of linking private sector expertise to public sector goals been achieved?
- Can/should PPPs be characterized/grouped/encouraged to communicate according to the field in which they are working, the types of products they are developing or their approaches to meeting need? Do we need to consider vaccine development as fundamentally different to drug development?

Figure 1. Successfully meeting needs



Session II. Determining and managing the portfolio

- Have existing PPPs articulated well defined product profiles/characteristics that they are working towards?
- How do PPPs select products within their portfolio, particularly those at different stages of development? Are they the best possible scientific leads? Did existing PPPs begin with an assessment of the field to allow conceptualization of a portfolio or did they start with those candidate products that were available to them?
- Does the PPP have access to, or ability to leverage, the best platforms, knowledge and expertise? What are the obstacles to accessing the most promising prospects?
- Does the PPP have sufficient financial resources to fulfil its determined niche?
- Do the PPPs feel that there is a critical mass of in-house staff necessary for efficient operations and, if so, what is it?
- How does a PPP define priorities and relative budget allocations within its portfolio?
- To what extent is this influenced by the PPP's partners/funders?
- How does a PPP determine the quality of its portfolio? Is this done by evaluating product leads within the portfolio or by evaluation of the field?
- Do they know what fraction of all promising candidates are in their portfolio?
- What is the governance structure of the PPP?
- Is there a clear business plan? Are the defined goals achievable?
- How are partners identified? If a good scientific proposal is developed how does the PPP ensure that there are appropriate partners? Does the proposal specify what inputs are expected from each partner? Are roles and responsibilities clearly defined? Are there tensions between public and private sector partners?
- Have PPPs developed via a planned partnership based on defined roles and expertise needs or by contracting for services with the private sector as required?
- How do PPPs manage their project activities?
- To what extent are private sector business practices used?
- Is there a difference in management between PPPs that are independent entities and those that are hosted by other public sector bodies?
- How does the PPP balance operational quality with positioning for their own visibility?
- Is advocacy needed in the PPPs' field of operation? If so, with whom and at what stage?
- What financial management mechanisms have been

instituted? Does the Board have an audit committee?
- Are the management, operational and financial mechanisms of PPPs transparent?
- Do existing PPPs fully use their staff and partner resource capacity/capability? Is there scope for sharing resources between PPPs in the same field or those facing similar downstream issues?
- How do PPPs define and monitor success? Have unequivocal, scientifically based milestones been established at the outset within realistic timelines?
- Is success determined solely by achieving milestones in the development of a specific product or also by reviewing the status of similar products being developed by others? Has it stimulated others to work in this area or are there better products now under development? Does a portfolio approach make it easier to discontinue specific products?
- What review procedures have been established? Are the PPP's activities reviewed in-house or by a panel of independent experts? If the latter, how frequently do they meet and what is their remit? Does the review committee include private sector expertise? Do donors serve on review bodies?
- When and how is the balance of activities determined and assessed? Are there rigorous and robust mechanisms to maintain a balanced portfolio? Have criteria been developed to assist in determining when development of a product should be stopped? Is the PPP willing to stop product development if significant difficulties have arisen or better products are likely to be available from others in a similar time frame?
- Is there a difference in review mechanisms between PPPs that control everything in-house and those that work through a group of partners?

Session III. Planning from discovery research to introduction

Upstream

- Are sufficient promising candidate products available for the PD PPP to create a meaningful portfolio? If this is a limitation, how serious a problem is it? What does the PPP currently do to overcome the problem?
- Does the PPP have routine contacts with the basic research community related to its disease? How?
- Does the PPP currently play a role in fostering very early research on possible product concepts/candidates? How could it be helped to achieve better access to early product concepts by links with both academic and pharma partners?
- Is there a need to strengthen R&D capacity in developing countries so the PPP has more partners in disease-endemic countries (DECs)? Is this currently regarded as a PPP responsibility?
- Do PPPs consider that they are developing products for the poor in developing country environments or do they start by considering the science and assume that the downstream issues (including suitability for DEC use) can be resolved later?
- Are developing country stakeholders involved from the outset? (Everybody will say, "Yes", but the question should also be asked: "Is research capacity strengthening one of your primary goals or is it a potentially useful by-product to the way you work?")
- How do PD PPPs currently handle proposals that are too early for them to fund or involve unproven approaches?

Midstream

- What role does the PPP plan (or need) to take in clinical trial capacity strengthening, including developing ethical review bodies and ensuring GCP in trial implementation?
- What collaboration is possible between PPPs to maximize use of clinical trial sites or other development expertise?
- Who should fund and take the lead in strengthening:
  - — ethical review capacity?
  - — clinical trials capacity (to pivotal licensing standards)?
- Do any mechanisms currently exist to coordinate funder support for these capacity strengthening efforts? If not, who could take the lead in developing more coordination?
- Are public sector partners adequately engaged – at this stage – to expedite:
  - — ethical review for trials initiation?
  - — regulatory approval?
  - — demand estimation?
  - — policy formulation?
  - — uptake?

Downstream

- Do PPPs evaluate downstream requirements, e.g., manufacturing capability, product stability and storage requirements, product cost, product registration, demand creation, donor/government purchase, health system service delivery capabilities, etc.? If so, how?
- Do PPPs include these downstream requirements in their business plans? If not, why not?
- As phase III trials begin, are parallel activities planned and budgeted for demand creation, financing and introduction? Do they begin to address service delivery mechanisms where they either do not exist or do not function adequately for the type of product under development?
- Has the PPP identified downstream stakeholders as partners or members of review bodies? If so, at what stage are they involved?
- How does the PPP address final product cost and transfer of technology? Where a PPP is built on inventions from a patent holder (for example, a small bio-pharma company), how are agreements made with the IP holder on final product cost or the right to seek other producers?
- What collaboration could/should be expected across PPPs to achieve downstream goals? Could any collaborative mechanisms be considered?
- How do PPPs handle the situation where (public sector) delivery systems are not functioning well and hence likely to reduce the public health benefit of its outputs?

Session IV. Financing the PPP

- What has the financial contribution of the private sector to the PPPs' activities been? Can in-kind support be quantified?
- Does the PPP receive unearmarked funding? Has demonstration of good performance been the principal reason for continuation of such funding or has it been aided by having a portfolio of products?
- Does the PPP have one or multiple donors? If multiple, do the donors have different funding conditions and/or expectations?
- Was initial funding based on a single product or on the development of a portfolio?
- What funding assumptions have been made in the business plan? Are the financial projections adequate to achieve end goals? How far has the PPP succeeded in meeting those projections, in terms of actual or pledged funding?
- Do multiple donors have different funding cycles/conditions? If so, how are these reconciled?
- Since most PPPs have different financing needs or approaches to their needs, is there a way to achieve 'equivalence across PPPs' for comparative review? How can estimated budgets for products at different stages of development be compared?
- How are financial needs linked to the perceived role of the PPP?
- How do different operational models affect actual/perceived financial needs?

Value for money and related donor issues

- To what extent do bilateral funders consider that PPPs 'misdirect' funds to the commercial/private sector?
- How do funders know that they are getting value for money? Do they have access to the outcomes of the PPPs' review process as well as independent evaluations from the field? How do donors determine their risk profiles? How do they know their contribution is making a difference?
- Do funders include downstream issues in their 'value' reviews?
- Even if it is acknowledged to be important to invest in a given field, how does the funder know that its contribution will make a difference?
- Do funders attempt to link funding to an identified lead that is likely to achieve its objective or will they provide unearmarked funding?
- Is there an optimal mechanism for funders to make investments in order to achieve best value?
- Can funders be realistically expected to provide the necessary funding to all ongoing PPPs or is there a need for some form of systematic review across and within fields of activity? If so, who could/should do this?

ANNEX 8

Background papers' key messages
(by sessions)

SESSION I

Opening of the workshop

Roy Widdus
Initiative on Public-Private Partnerships for Health
Geneva, Switzerland

The workshop is a unique opportunity to consider collectively three important topics:

- How can we most usefully define and conceptualize the 'field' of improving tools for control of neglected diseases?
  - If the ultimate objective is public health impact, 'access' issues will need to be addressed; the PD PPPs may have to encourage action on these issues if no one else is doing so adequately.
  - How do we estimate future potential public health benefit?
- How can we improve communication and understanding among implementers and funders?
  - Especially **across** the PD PPPs and **along** the research-development-access continuum.
- How can we make future decisions based on better information?
  - Need to identify what to monitor and analyse further.

The issues related to these three questions can be grouped as those that relate to the broader field, and those that relate to the individual product development partnership.

It is perhaps more important to decide how to continue the information exchange and analysis than to believe that all questions can be decided at this meeting.

SESSION II

Portfolio management in pharmaceutical companies and PD PPPs

Portfolio management in the pharmaceutical industry

(Esther Schmid, Pfizer, UK)

- R&D is inherently risky and therefore many simultaneous discovery efforts are needed if a medicine is to be produced.
- Key performance indicators are used to build and actively manage a portfolio so that it has a high chance of success.
- Portfolio management limits risk, time to market and costs.

The emerging landscape of public-private partnerships for product development

(Alison Sander, Consultant, USA and Roy Widdus, IPPPH, Switzerland)

- Portfolio management is critical because product development is such a risky and lengthy process. Estimates of the time and cost required to develop a drug in the private sector range from US$400–650 million and 8 to 15 years.
- Portfolio management has two components – diversification (reduced reliance on a small number of candidates with similar characteristics) and robust portfolio management processes (to ensure that candidates which do not meet the desired specifications are actively weeded out).
- A key issue with neglected diseases is the level and perspective from which portfolio analysis is applied. One could view all 25 PD PPPs developing products for neglected diseases as a single portfolio. Port-

folio management is also a tool that can be applied to the product portfolios of individual PD PPPs. The key issue is what is being optimized.

Demonstrating value: Performance metrics for health product development public private partnerships

(Mark Pfitzer, Foundation Strategy Group, Switzerland)

- Comprehensive performance metrics go beyond funds raised and disbursed, and demonstrate how progress on value-added activities impacts R&D and operational costs.
- PD PPPs exploit their legitimacy and knowledge, and reach advantages to create value in four ways by:
  - — Building unique capabilities and platforms to attract and select the most promising projects
  - — Improving their partners' research capabilities
  - — Mobilizing funds in line with portfolio and organizational developments
  - — Enhancing knowledge and knowledge dissemination among research partners and the broader public health actors involved in turning new products into health impact.
- Performance dashboards metrics that highlight a PPP's primary added-value activities will both encourage donors and focus the PPPs on the activities that will most contribute to their success.

SESSION III

The role of PD PPPs and the environment necessary for their success

The current research-to-development 'hand-off' process for product concepts/candidate products and possible improvements in it

(Solomon Nwaka, MMV, and Roy Widdus, IPPPH, Switzerland)

- Investment in basic research will only benefit patients if it is efficiently translated into early candidate products; however, this process is currently sub-optimal.
- Various approaches to improving this 'translation' have been identified.
- New funding mechanisms, aimed at public, or public interest, institutions are warranted as part of a comprehensive approach to improving tools to combat neglected diseases.

The emerging landscape of public-private partnerships for product development

(Alison Sander, Consultant, USA and Roy Widdus, IPPPH, Switzerland)

- While each PD PPP has a unique mission and set of challenges, strategic and operational choices can influence both the cost to achieve a mission and the likelihood of success. Our paper looks at a range of 16 variables and extracts the factors that are thought most likely to be critical for success.
- At the level of individual PD PPPs, success will probably be a function of strategic fit between eight variables:
  - — the challenge identified
  - — the readiness/complexity of the science
  - — the willingness of donors to support the venture
  - — the match with downstream needs
  - — the quality of management
  - — the robustness of the portfolio
  - — the level of independent oversight
  - — the quality of strategic partnering.
- In addition to these eight factors, it is important that each PD PPP manage the following three elements :
  - — Finding the right balance between a concern about upstream science and downstream access issues
  - — Managing the multiple interface points where hand-offs are expected or where different contractors are involved
  - — Developing intellectual property and contract agreements that balance in the long term with the flexibility required during the development phase.
- The ability to attract other sources of funding over the long term will also depend on the view of the overall PD PPP field. It is important that donors and PD PPPs develop projections of the funds required for product development, define interim metrics of progress, work to attract other donors to the field, and look for places where sharing platforms may bring efficiencies to the field.

Ethical review capacity: Country needs, role and responsibility of partners and researchers

(Rose Leke, University of Yaoundé, Cameroon)

- Ethics review committees: Weak, ineffective, inadequate training, no access to international guidelines – interpretation, lack of standard operating procedures (SOPs).
- Informed consent – western perspective: Individual/personal rights in Africa: family, community. True informed consent often questionable.
- Collaboration – partnerships
  - — Collaborator-donor, who owns research
  - — Rights of 'receiver': financial, publication, property rights
  - — Overheads blind the review process
  - — Accountability.
- Advocate for sound ethical review practices in Africa.

What else needs to be in place for PD PPPs to do their tasks effectively: Clinical trials capacity

(Ebi Kimanani, International Biomedical Research in Africa [IBRIA], Kenya)

- Pipeline: Globally, there are over 300 products in development for HIV, 45 for malaria and 22 for tuberculosis.
- Current capacity: A gap exists between the clinical testing capacity required to support this pipeline and what is available in sub-Saharan Africa.
- Way forward: Funding, scientific and regulatory leadership are needed to build infrastructure, human resources and essential systems to meet this demand.

Emerging lessons in preparing for uptake of new vaccines

(Gargee Ghosh, Center for Global Development, USA)

- Achieving health impact requires not only product development but successful product introduction and widespread, sustainable uptake
- Successful product introduction requires planning that starts while the product is in the development pipeline – PPPs need to start thinking about this today to avoid wasting precious time later
- Planning for introduction requires not only explicit focus but also a new set of skills, analyses and approaches that the global community will need to develop.

The current research-to-development 'hand-off' process for product concept/candidate products and possible improvements in it

(Solomon Nwaka, MMV, and Roy Widdus, IPPPH, Switzerland)

More public sector attention needs to be paid to mechanisms and resources to assist in the translation of scientific innovation into practical, product-directed discovery and development. Ideally public-private partnership is also required for this upstream activity where we need to build capacity, with equal attention to providing opportunities in developing as well as developed countries

- Further evidence will be required downstream of product registration to justify public sector purchase of products and their incorporation into essential drug lists, national policies and guidelines. Preparation for such studies will be required during the later stages of product development and the transition needs to be carefully managed
- The overall process should be seen as one of providing evidence to make public policy decisions, not of 'promoting' one product over another. The process of evidence generation needs to ensure an appropriate level of data ownership at the country level and utilize and develop research capacities.

SESSION IV

Financial aspects of product development for neglected diseases

What is the current financial situation for PD PPPs using the portfolio management approach?

(Adrian Towse, Office of Health Economics, UK)

- Responsibilities: A key question is whether portfolio management responsibilities should lie with the donor or with the PD PPPs
- Performance: It is difficult for donors to assess performance when some PD PPPs do not have quantifiable objectives
- Supply constraints: Portfolios need to be large enough to deal with failure, but only take projects justified by scientific merit
- Cost estimates: Differences in cost estimates for clinical phases highlight the need for greater transparency in PD PPPs projections

- Capacity building: The need to estimate infrastructure investment for conducting clinical trials is key
- The financing gap is large between the funding available to PD PPPs and the finances needed to get products to market.

The costs of developing vaccines: Case study of VaxGen's candidate HIV vaccine

(Donald P. Francis, Brisbane, CA, USA)

- With the current for-profit paradigm of pharmaceutical development, the power of modern science will not be harnessed to prevent disease
- AIDSVAX, VaxGen's candidate HIV vaccine, has required over 20 years of development and cost approximately US$200 million, but is far from complete
- The problem is not the lack of scientific/technical tools available for vaccine development but rather the will to finance and use them

The cost of trials and manufacturing process development for vaccines

(Jerry Sadoff, Aeras Global TB Vaccine Foundation, USA)

- Field sites require building good clinical practice infrastructure and availability of enough valuable cases of the disease being studied
- The best way to satisfy both these requirements is to perform longitudinal cohort studies in target populations that are similar to vaccine studies in terms of enrolment, follow-up, monitoring and data management
- Accurate estimates of vaccine uptake curves based on product profiles and projected prices are required five years before vaccine licensure to ensure capital investment in properly sized factories so as to prevent tragic delays in vaccine availability.

PD PPPs for diseases of poverty: Are there more efficient alternatives? Are there limitations?

(Robert G. Ridley, WHO/TDR, Switzerland)

- Completely private sector and completely public sector models exist for product development of diseases of poverty, but history indicates that, so far, PPPs have delivered new tools more effectively for these diseases and at a relatively low cost. Synergies of infrastructure and human expertise account for this enhanced cost-efficiency
- Despite increased funding for diseases of poverty, resources are still extremely low, and activities are fragmented compared to the huge 'economies of scale' of major pharmaceutical companies. The community needs to ensure better agreement on target product profiles and better coordination of effort without creating 'monopolies' whereby one group effectively controls all R&D activity
- The building of essential research, organizational and managerial capacities, particularly in the developing countries, is essential to the long-term, sustainable generation of relevant new and innovative products to address diseases of poverty. Research capacity building and broad 'stakeholdership' involving developing countries should be integral to our activities, and not just perceived as 'nice to have'.

SESSION V

Possible innovative approaches to funding product development for neglected health problems

PPPs and product development: Innovative financing opportunities and the need for a 'business case' approach

(Amy Batson, World Bank, USA; Raj Shah, Bill & Melinda Gates Foundation, USA; Chris Gingerich, Consultant, Bill & Melinda Gates Foundation, USA; and J. Niels Rosenquist, Consultant, World Bank and GAVI)

- Capital markets may provide access to new sources of investor money, and may provide other tools to optimize existing financial flows
- The ability to attract investor money is based on the presumption of a guaranteed future market for the product in question
- PD funding is not generally a priority for traditional sources of major development financing
- There are, however, emerging opportunities among new multilateral funds and new programmes in major development financing institutions
- Business case-style analyses and funding proposals focus on communicating return on investment (financial and/or programmatic) to potential funders
- As PPPs become more competent at business case-style analyses, they will be better positioned to obtain financing from any source.

Do guarantee purchase mechanisms serve as an incentive for product development?

(Gargee Ghosh, Center for Global Development, USA)

- Guarantee purchase mechanisms can be designed to provide market assurances that help mitigate some of the critical risks inhibiting product development today
- The work of the Pull Mechanisms Working Group shows that these mechanisms are legally and practically feasible, and would have an effect on some firms' investment decisions
- These mechanisms need to be part of a comprehensive product development strategy – they are not (and should not be used as) a 'silver-bullet solution'.

ANNEX 9A

Estimates of the medium-term financial resource needs for development of pharmaceuticals to combat 'neglected diseases'

Adrian Towse, Jorge Mestre-Ferrandiz, and Olwen Renowden (Office of Health Economics, UK)

Executive summary

This paper has been prepared for a workshop organized by the IPPPH on 15–16 April 2004. The focus of the brief is to analyse the financing needs of a number of portfolio-based PD PPPs. In particular we were asked to inform donors of the potential funding gap which PD PPPs might face over the medium term if they are to achieve their stated product development objectives.

If donors are to achieve new licensed drugs and vaccines for neglected diseases, then they have to deal with the low likely success rates of individual projects. The best way to do this is through a portfolio of investments. The PD PPPs are better placed to manage a portfolio of projects than individual donors. The question then arises as to how much money the PD PPPs need to achieve their objectives in managing these project portfolios on behalf of donors.

The PD PPP estimates of discovery and development costs and project attrition rates show major differences in both the discovery/pre-clinical and the clinical phases. It is not clear why there is such variation and there would be benefit in some shared understanding between donors and PD PPPs as to the basis of project cost projections across different PD PPPs. In particular we note that:

- Statistical data on failure and attrition rates are very poor for vaccines;
- Two important areas of cost need more examination – manufacturing costs and investment in clinical trial infrastructure;
- There is a need for a much better understanding of the potential value of in-kind benefits from industry and others.

In spite of the difficulties of estimating potential costs it is clear to us that there is a large gap between the funding available to PD PPPs and the finances they are likely to need to get products to market. Donors and PD PPPs need to improve their understanding of the likely size of the gap and how it might be filled.

We used three approaches to arrive at estimates of this gap:

1. Using PD PPP estimates of the cumulative funding pledges they have received and a mix of sources for estimates of their cumulative resource requirements, we found that for four PD PPPs (TB Alliance, DNDi, MMV, IAVI) the gap is around US$1.2 billion.
2. Calculating the development costs of existing PD PPP portfolios we estimated a shortfall of US$720m for vaccines and US$730m for drugs, making a total of US$1,450m. It should be borne in mind, however, that the PD PPPs are still building their portfolios and the number could be higher;
3. Our third rule of thumb was to assume that each of the 14 PD PPPs included in our analysis brought one product to market at an average out-of-pocket cost of US$160m (roughly in the middle of the US$128m–192m range we found). This would involve costs of US$2.2 billion.

Using these three approaches we estimated the funding gap at between US$1.2 billion for four PD PPPs to US$2.2bn for 14 products, depending on the assumptions made, which include:

- which PD PPPs are included;
- size of portfolio;
- attrition rates and costs; and
- any offsetting contributions in-kind.

Introduction

Context

The product development public private partnerships (PD PPPs) were set up to help address a market failure – the lack of commercial incentive to undertake R&D into drugs, vaccines and diagnostics for diseases of poverty. The problem of failure is easiest to highlight in the cases of drugs and vaccines. Discovery and development costs run into hundreds of millions of US dollars. Yet patients in less developed countries and their governments do not have the money to pay prices that will enable these R&D costs to be recovered.

Donor money – public, philanthropic or from nongovernmental organizations (NGOs) – is therefore needed to fund R&D into these diseases and/or to provide incentives for the private sector to undertake this work. Expertise in drug and vaccine development lies with industry. Hence the attraction of forming PD PPPs as not-for-profit bodies standing between the public and private sectors but including both as stakeholders, seeking to work with industry to develop products to tackle key global health problems (Widdus et al., 2001).

There are other mechanisms to provide incentives to the private sector pharmaceutical industry, usually categorized into 'push' (reducing industry costs through grants, tax breaks, fast track approvals) and "pull" (creating effective demand, for example via global funds[1] and advance price and purchase commitments). These are not mutually exclusive – most PPPs plan to license products to the private sector where there is sufficient commercial incentive for them to do so. Understanding the potential role of other 'push' and 'pull' measures to involve the private sector is crucial to understanding future PD PPP financing requirements (as we discuss later) and to improving the viability of PD PPPs as a mechanism to deliver new products (Kettler and Towse, 2002).

Because of the emphasis on product development and the high risks of failure associated with bringing products through the R&D process, most PD PPPs proceed with a number of projects, depending on the resources they have and the potential scientific value of the projects. This implicit or explicit portfolio approach is another important way in which PD PPPs differ from many of the other projects and organizations that donors fund. We return to this issue below.

[1] For example, GAVI / Vaccine Fund and GFATM.

Objectives/terms of reference

This paper has been prepared for a workshop organized by the IPPPH on 15–16 April 2004. The focus of the brief is to analyse the financing needs of a number of portfolio-based PD PPPs. In particular we were asked to inform donors of the potential funding gap which PD PPPs might face over the medium term if they are to achieve their stated product development objectives. The list of PD PPPs is in Table 1 below. The key elements are to:

- outline the product development objectives of the PD PPPs. What is the PD PPP saying it wants to

Table 1. The IPPPH list of PPPs

Focus of financial analysis	
DNDi	Drugs for Neglected Diseases *initiative*
MMV	Medicines for Malaria Venture
IAVI	International AIDS Vaccine Initiative
TB Alliance	Global Alliance for TB Drug Development/TB Alliance
Other portfolio based PD PPPs	
Aeras	Global TB Vaccine Foundation
IOWH	Institute for OneWorld Health
MVI	Malaria Vaccine Initiative
FIND	Foundation for Innovative New Diagnostics
SAAVI	South African AIDS Vaccine Initiative
EMVI	European Malaria Vaccine Initiative
HHVI	Human Hookworm Vaccine Initiative
IPM	International Partnership for Microbicides
MDP	Microbicide Development Programme
PDVI	Pediatric Dengue Vaccine Initiative
PPPs not included in the study remit	
Pneumo-ADIP	Pneumococcal Vaccine Accelerated Development and Introduction Plan
Rota-ADIP	Rotavirus Vaccine Accelerated Development and Introduction Plan
BVGH	BIO Ventures for Global Health

achieve and in what time frame (e.g. bring a vaccine to market by 2010)?
- identify the resources the PD PPP calculates it needs to deliver these objectives, including the assumptions made about the contributions of others (e.g., is there an assumption that industry or a government body such as USAID or the EDCTP will fund a phase III trial?);
- analyse whether we think this calculation is reasonable to deliver those objectives, and if not how much will be required;
- set out the resources currently committed by donors to the PD PPPs; and
- conclude as to the potential 'funding gap' that donors may have to fund if the PD PPPs are to achieve their product development objectives.

In the event, lack of data and time constraints have restricted our ability to deliver these terms of reference. Data problems encountered include distinguishing between product development costs and the costs of other PD PPP activities; relatively short-term financial projections given the length of time it takes to bring a drug or vaccine through the development process; the relatively immature state of the project/product portfolios in a number of cases (most PD PPPs appear to have no portfolio projections and only two – MMV and DNDi – have an explicit model of portfolios with expected success rates); and a lack of detail about assumptions made of expected in-kind or funding contributions from industry partners or other agencies. We must make it clear that this does not necessarily reflect a lack of responsiveness on the part of the PD PPPs. They are, for the most part, simply not currently geared up to make long-term funding projections based on a portfolio approach to achieving their product development objectives.

After discussion with IPPPH we revised our objectives in the light of the material available. The key aspect of our work is to help donors understand how to assess whether the PD PPPs have the financial resources to build portfolios of projects that will enable them to deliver their objectives.[1] We have therefore:

- focused on a subgroup of four PD PPPs for the financial analysis – MMV, IAVI, TB Alliance and DNDi. Where possible, the portfolio expectations and financial needs of the remaining PD PPPs are discussed;
- analysed why portfolios are important for donors and PD PPPs; and
- made recommendations to identify the issues donors may wish to address in respect of information needs for future decision-making to enable them to appraise progress and understand potential future funding requirements.

Method of working

In researching this paper we undertook:

- in-person interviews (with IPPPH, MMV, MVI and EDCTP) and telephone interviews (with MMV, DNDi, TB Alliance and SAAVI);
- a questionnaire survey (with responses from MMV, MVI, DNDi, TB Alliance and SAAVI);
- use of IPPPH to collect information on PD PPP objectives, finances and project/product portfolios. IPPPH surveyed the PD PPPs on our behalf;
- literature searches on drug and vaccine development costs. We were also given drafts of relevant studies prepared for the IPPPH workshop; and
- a review of earlier work we had undertaken looking at drug and vaccine development costs for PD PPPs.

The information gathered by IPPPH was key and we used their summary table as the basis of further investigations about the 'current' versus 'desired' portfolios of the PD PPPs. In telephone interviews, we asked the PPPs to verify the portfolio content data collated by IPPPH and we also solicited feedback on a number of other issues including the extent to which different activities would be funded using their own resources as compared to those of other parties, and funding gaps for product development through to 2007.

The relevance of a portfolio approach

Why a portfolio approach?

The PD PPPs have been characterized as requiring a portfolio of projects because of the high attrition rates in developing both drugs and vaccines. If the objective is to get products licensed, then enough projects need to be in the pipeline to compensate for failures.

If some risk is to be diversified, however, the projects that make up the portfolio need to be sufficiently dif-

[1] We are not in a position to comment on the scientific value of portfolios or projects.

ferent from one another in order that the probability of the portfolio delivering is greater than that of any one of its component projects. Portfolio management also raises important issues about the relationship between the donors and the PD PPPs and about the efficiency of managing a portfolio.

Diversifying risk

The greater the similarity between two projects (in scientific approach, for example), the more likely it is that they will either both succeed or both fail. The key to reducing risk is to combine projects that have different underlying characteristics. A distinction is usually made in the financial literature between systematic and unsystematic risk.[1] Systematic risk is the element of risk that is shared across projects and cannot be diversified. In the context of PD PPPs this might include:

- the disease area the PD PPP is tackling: it may be an inherently difficult or less difficult area scientifically;
- the technology (drug or vaccine): this may also be inherently more or less challenging;
- scientific approaches taken in particular projects (e.g., choice of target);[2]
- management skills, including the ability to choose partners and subcontractors and to progress or terminate projects. These will affect the ability of the organization to deliver successfully.

Thus a PD PPP could diversify risk by working on more than one technology and/or in more than one disease area. However, it may not be efficient for it to do so (see 'Are there management efficiency gains?' below). More importantly it is fundamental to understand that the real problem of managing risk is at the donor level. If the donor's objective is to tackle HIV/AIDS, malaria and tuberculosis (TB) and other diseases of poverty, then it is not possible for the donor to achieve that by diversifying into other disease areas.[3] The issue then becomes one for the donor as to whether to fund one or more organizations to tackle each of these diseases and whether to fund individual projects or a portfolio.

Implications for the relationship between the donors and the PD PPPs

Whether or not a PD PPP has a portfolio approach has significant implications for the relationship between the PD PPP and its donors.[4] The problem for the donors is how to ensure that the PD PPPs – as the donors' agents – are doing the best job they can with the resources they have. If the PD PPPs have a portfolio approach then it is possible for the donors to adopt a more 'arm's-length' approach and look at whether the PD PPP is delivering the final outputs from the pipeline in terms of licensed drugs/vaccines. It does not need to get involved in the detail of how individual projects are progressing within the portfolio, although it will want to be satisfied that effective management is in place and that there are processes to ensure the scientific quality of the portfolio. The analogy is with a large investor in a major pharmaceutical company. However, some donors may be used to minimizing the discretion they provide to recipients because they do not have confidence in their judgement. For them, the portfolio approach may require a change in attitude.

If, however, the PD PPP does not have a portfolio geared to achieve a specific flow of final outputs but has a much smaller number of projects, it is harder for donors to assess performance. In this case the analogy is with a venture capital investor. There is a high risk that all of the projects will fail, but this does not necessarily mean that the PD PPP has chosen poorly or managed its projects badly. It does mean that the donor will have to manage its funding more actively. This is for two reasons:

- It is harder for the donor to understand whether project selection and management are working.
- There is a problem of asymmetric information: the PD PPP is much better informed than the donor

[1] In financial portfolio management the objective is to reduce the expected variability of financial returns relative to the expected mean return by diversifying unsystematic risk.

[2] Strictly what matters is the covariance of returns. A PD PPP could pick two alternative approaches whose success was mutually exclusive, i.e. they relied on opposite assumptions about the causes or treatment of the disease. If one worked, the other could not and vice versa. Choosing to undertake both of these projects would reduce risk. Of course both might still fail because, for example, neither analysis of disease pathways was accurate.

[3] They could, in principle, diversify into other ways of tackling these diseases. Presumably, however, prior analysis suggested that funding R&D was a cost-effective way of achieving valuable global health gain.

[4] The branch of economic theory that analyses relationships of this type is called principal–agent theory.

about the likely prospects of the project. If it has very few other projects then it may be tempted to present a more optimistic view of a project's ultimate likely success than the underlying science and results to date suggest.

Typically venture capital organizations overcome these problems through staged payments linked to success criteria that can be independently verified. However, they also usually employ highly skilled staff to manage their investments.

Are there management efficiency gains?

Are disease- and/or technology-specific portfolios the best way to proceed? It is probable that scientific expertise has a strong disease- and/or technology-specific element to it. Thus there are likely to be gains in efficiency from specialization. Most PD PPPs do specialize in either drugs or vaccines or diagnostics, and are disease specific. Only DNDi and IOWH cover several disease areas. DNDi focuses not only on kinetoplastoid diseases (Chagas disease, leishmaniasis and sleeping sickness) where there are scientific links – but also on malaria. IOWH is also involved in these diseases – plus diarrhoeal disease and intestinal worms.

There may also be spillover effects, i.e. benefits from undertaking more than one research project within a single organization. Studies (e.g. Henderson and Cockburn, 1996) suggest that research can be more productive in total when projects are within one organization than when they are split across organizations.

Do PD PPPs need to have portfolios?

It is important to understand that if the donors want to achieve certain objectives (such as new, licensed drugs/vaccines for neglected diseases) then they have to deal with the probability of individual projects' low success rates. They need to manage their risk relative to the expected gains from successfully tackling these global health problems. The best way to do this is through a portfolio of investments. The question is whether the portfolio approach rests with the donor or with the PD PPPs. Arguably the PD PPPs are better placed to manage a portfolio of projects. Donors, with one or two exceptions, do not have the resources to manage individual projects or to deal appropriately with high failure rates. Their culture may also not be appropriate. Project failures may tend to be misinterpreted as organizational failures and less than optimal funding put in place as a result.[1]

Do the PD PPPs have portfolio approaches?

Table 2 sets out the productivity objectives of the PD PPPs, while Table 3 summarizes their current portfolios in terms of the numbers of projects at each stage of development. In total there are 79 projects at various stages of development. It is clear that most of the PD PPPs have portfolios of projects and objectives that require a portfolio approach. However, we would make the following points:

- Some PD PPPs do not have quantifiable objectives. This will make it harder for donors to assess performance.
- Not all PD PPPs have had the time or resources to establish a portfolio that will enable them to meet their objectives.
- There is no point in establishing quantifiable objectives that are out of line with the funding required to achieve them. In particular, if the portfolio is too small relative to the objective because of a lack of funding, there will be pressure on the PD PPP to keep unpromising projects going in the hope of achieving their objectives. Having a portfolio that is large enough to deal with project failure is crucial.
- Conversely there is no point in pushing PD PPPs to hold a portfolio that is larger than justified by the scientific merit of the projects available. This will simply result in larger failure rates later in the development process.

Overall we conclude that portfolio approaches should be used at the PD PPP level and that donors should seek to align funding with objectives; for example, if a large portfolio is not realizable then quantifiable objectives should be adjusted downwards accordingly.

[1] For example, project failure in a portfolio management context may lead to resources being switched over to back the remaining projects. In a non-portfolio management organization, project failure may be taken as a sign that the whole area or the organization is high risk and so lead to disinvestment.

Table 2. PD PPP productivity objectives

PPP	Productivity goal (preferably quantitative)
Aeras	One TB vaccine within 10 years
DNDi	Six to seven new registered drugs by 2015
EMVI	To bridge the conceptual and operational gaps between the bench product (i.e. candidate molecules) and further validation, limited production and clinical testing
FIND	To accelerate development, evaluation and appropriate use of affordable diagnostic tools (TB diagnostics)
HHVI	Reach phase II clinical trials by 2010
IAVI	Eight to 12 novel vaccine candidates into clinical trials, and advance the best two or three to final-stage testing (phase III) by 2007
IOWH	• To obtain regulatory approval for Paromomycin in India by 2005 for visceral leishmaniasis • Chagas disease K777 • To develop one drug or vaccine against bacterial-induced diarrhoea • Malaria
IPM	To accelerate the discovery, development and accessibility of safe and effective microbicides
MDP	To complete phase I trials of one or more microbicide candidates by 2005 and phase III by 2008
MMV	One new drug every five years, with the first one by 2010
MVI	To accelerate the development and accessibility of safe and effective malaria vaccines
PDVI	Reach phase III efficacy studies by 2006
SAAVI	To develop an affordable and effective HIV vaccine as soon as possible
TB Alliance	To scale up the pipeline to deliver improvements in TB therapy. First new drug for registration by 2010

Source: IPPPH, based on responses from organizations where received, or from their websites, as of early 2004

Table 3. PD PPP portfolios

PPP	Portfolio			
	Current			
	Pre-clinical	Phase I	Phase II	Phase III
Aeras		2		
DNDi***				3
EMVI				
FIND		1	1	1
HHVI	2			
IAVI	2	2	1	
IOWH	3		1	1
IPM				
MDP		1		1
MMV	14 in discovery	4	2	2
MVI	8	6	1	
PDVI				
SAAVI**	6	0		
TB Alliance*	10	0	1	0
TOTAL	**47**	**16**	**7**	**8**
Of which drugs	26	8	5	8
Vaccines	19	8	2	0

Sources: IPPPH, based on responses from organizations where received, or from their websites, as of early 2004; and interviews.

* TB Alliance anticipates a portfolio of three phase I trials and that their current phase II trial will enter phase III before 2007. Their portfolio also includes platform-related investments.

** SAAVI have none of their own products at phase I yet but collaborate on two projects which are at this stage.

*** DNDi have two malaria drugs in phase III partly financed by the European Union.

A methodology for estimating financing needs

A model of R&D portfolio cost for PD PPPs

Five elements are necessary to build a model to estimate PD PPP R&D costs over a defined period:

- Understanding target output objectives (in terms of licensed new products per annum).
- Estimating attrition or failure rates for projects at each stage of the R&D process.
- Identifying the expected cost per project at each stage of development.
- Deducting those parts of the development process that the PD PPP will not be funding itself, i.e. in-kind contributions from industry or other bodies.
- Specifying the resultant costs per time period of the projects that will be under way during the period under consideration.[1]

In-kind contributions are discussed in the next section. These might comprise the possibility to obtain projects/products that are already part of the way through the development process at below cost, or the undertaking of activity by a third party at less than the "full price" they would expect as a commercial subcontractor.

A simple way of starting to understand what financing might be required and the complications involved in deriving estimates is to look at the cost of bringing a drug/vaccine through the R&D process to obtain a licence. We look at the PD PPP estimates of attrition rates, costs per project, timelines and the implied total cost of developing a drug or vaccine. We begin by looking at the DiMasi et al. (2003) estimate of the costs of drug development, which are based on actual drug development costs for a sample of products.

The DiMasi et al. estimate of the costs of drug development

The DiMasi et al. (2003) estimate of US$802 million (in 2000 US dollars) for the costs of bringing a new drug to market is much cited. Table 4 sets out the basis upon which it is built. It comprises:

- actual mean out-of-pocket costs for phases I–III for a random sample of 68 products developed by 10 major R&D–based companies (US$132.6m);
- the use of overall R&D spend data to include in pre-clinical development (e.g., discovery) costs of 30% (adding US$26.0m to the cost);
- success rates for these projects, i.e., the probability of moving from one stage to the next (transitional probabilities), giving an expected cost of developing a drug of US$86.6m; and
- adjusting for failures using the overall success rate from entry into phase I to successful New Drug Approval (NDA) of 0.215 to give total out-of-pocket costs of US$403m.

The balance of cost (US$399m) is represented by the opportunity cost of capital. This is not relevant to the PD PPPs which do not have to provide a return on capital other than via achieving a high social benefit to their activities.[2]

The table shows that 4.65 products need to enter clinical development in order to achieve one licensed product. The structure of this model is used to estimate PD PPP development costs using PD PPP-specific data on costs and attrition rates.

Estimates of attrition rates by PD PPPs

We obtained estimates of PD PPP specific attrition rates from the following sources:

- MMV Business Plan 2003–07 (2003)
- TB Alliance commissioned study, *The economics of TB drug development* (2001)
- DNDi Business Plan (2003)
- an analysis of vaccine attrition rates by Struck (1998), which looks at the probabilities of success from an analysis of 591 vaccine candidates between 1983–94. It may, therefore, not be an accurate representation of the likely success rates of current vaccine candidates
- Boston Consulting Group (BCG study, *The Economics of Microbicide Development: a case for investment.*

[1] This can be done with various degrees of sophistication to take account of the uncertainty around both success rates and costs. One approach is to use probabilistic sensitivity analysis, whereby each parameter is assigned a distribution, and project success/cost results associated with simultaneously selecting random values from those distributions are recorded in a Monte Carlo simulation of the model. MMV used this approach in developing its business plan.

[2] Of course, there remains a social opportunity cost of capital supplied to the PD PPPs and this may be higher than that supplied to the pharmaceutical industry. Hard-pressed donor budgets may have a number of alternative uses, many of which may yield high social returns.

Table 4. DiMasi et al. estimates of the numbers of compounds and amount of expenditure required by phase to take one successful compound to market approval

Stage	Pre-clinical	Phase I	Phase II	Phase III	LAT*	Total
Transitional probabilities	1.0	0.71	0.442	0.685	0.685	0.215
Number of compounds required	4.65	4.65	3.3	1.46	1.46	1
Average cost per phase per compound (in US$ millions)	26.0	15.2	23.5	86.3	5.2	156.2
Expected cost per phase (in US$ millions)	26.0	15.2	16.7	27.1	1.6	86.6
Total cost per successful compound (in US$ millions)	120.9	70.7	77.6	126.0	7.6	402.8
Percentage of total out-of-pocket R&D spend	30	18	19	31	2	100

* LAT = long-term animal testing

Table 5. Transition probabilities of success by phase

	MMV	TB Alliance	DNDi	Vaccines (Struck)	DiMasi at al.	BCG
Discovery						
— early	0.3					
— lead identification	0.65		0.55			0.3
— lead optimization	0.55					
Pre-clinical	0.55	0.1	0.63	0.56		0.5
Phase I	0.7	0.3		0.72	0.71	0.75
Phase II	0.5	0.5	0.24	0.79	0.442	0.75
Phase III	0.65	0.65		0.68	0.685	0.25
Registration/approval	0.95					0.90
NDA overall	0.0134	0.0098	0.08	0.22	0.215	0.019
NDA clinical phases only	0.2275	0.098	0.24	0.39	0.215	0.1406

Sources: MMV (2003), GATBDD (2001), DNDi (2003), Struck (1998), DiMasi et al. (2003), BCG.

We also draw on earlier work by Towse and Jamison (2003) and Towse and Mestre Ferrandiz (2003). For comparative purposes we also included the DiMasi numbers. The results are set out in Table 5. Some similarities in the numbers are apparent, but there are also significant differences.

Estimates of cost per phase by PD PPPs

Using the same sources as above, except for substituting the IAVI Scientific Blueprint numbers for the Struck attrition rates, we again get a significant range of cost estimates for each phase of development (Table 6).

Possible sources of cost differences

There are major differences in cost in the discovery/pre-clinical and clinical phases. We do not have enough information to understand possible reasons for the differences in the discovery and pre-clinical phases. However, differences in cost in the clinical phases appear to reflect differences in the numbers of trials, lengths of trials, numbers of patients per trial and cost per patient per trial.

Whilst we would expect these to vary by disease area, and to be different for vaccines as compared to pharmaceuticals, it is not clear why there is such variation. It would be beneficial to both donors and PD PPPs if

Table 6. Estimates of cost per phase by PD PPP (in US$ millions)

	MMV	TB Alliance	DNDi	IAVI	DiMasi et al.	BCG
Total discovery and pre-clinical	**8.33**	**18.6**	**16.2**	**20.0**	**26.0**	**4.5**
Phase I	1.58	0.6		7.0	15.2	2.0
Phase II	1.15	3.4			23.5	3.0
Phase III	9.5	22.6		30.0	86.3	46.0
Total clinical	**12.23**	**26.6**	**24.2**	**37.0**	**125.0**	**51.0**
Other	1.5	8.0		50.0	5.2	1.0

Sources: MMV (2003); GATBDD (2001); DNDi (2003); IAVI (2000); DiMasi et al. (2003); BCG

they understood the basis of the cost projections across different PD PPPs.

Drug versus vaccines: clinical development costs

One source of difference in costs is that between vaccines and drugs. The major differences between drugs and vaccines include:

- *Failure rates and attrition data.* Statistical data on failure and attrition rates are very poor for vaccines. This is largely because of the small portfolio sizes but also reflects the belief that all the 'easy' vaccines have already been developed and, therefore, future failure rates may not resemble those seen in the past.
- *Portfolio size.* Typically, a commercial operation may screen and conduct pre-clinical testing on up to 100 new chemical entities (NCEs). Vaccines, by contrast, may be tested with only two or three variants in a 'portfolio'. Vaccine development, if unsuccessful, may be abandoned at pre-clinical stages.
- *Risky science.* The efficacy and toxicity are greater unknowns in a vaccine trial than in a drug trial. This is another important reason why the 'hurdle costs' of taking a vaccine into clinical testing may be much greater than for a drug. A candidate vaccine relies less on transferable knowledge in previous trials.
- *Trial size and cohort studies.* Since the main cost of any clinical trial is the per-subject cost, the necessity to run much larger trials for a vaccine than for a drug increases the cost significantly. Vaccine trials require that healthy subjects are included in the sample. Preventative trials (and trials for TB drugs for complex reasons) typically need much larger study populations. Thus drug trials, such as those anticipated by MMV, may cost around US$10 million because the numbers of patients are assumed to be small (fewer than 2,000) and the cost per patient relatively low (below US$10,000 including the costs of analysing the trial). A large vaccine trial for a new HIV vaccine, however, could cost between US$50 million and US$120 million[1] and possibly more. This may include no allowance for capacity building or infrastructure. From the financial resource requirement perspective, the size and cost of clinical trials is the most important difference between vaccine and drug development.
- Infrastructure costs. When estimating the clinical development costs for a vaccine or NCE, it is important to distinguish between the costs of conducting a trial and the cost of putting the infrastructure or capacity in place to run the trial. Scientists agree that vaccine trials require the final factory product and hence capacity building is required much earlier in the clinical trial phase than with drug development. This can essentially be treated as a sunk cost if the trial fails. A detailed analysis of capacity-building costs is presented in Annex 9k (J. Sadoff).

Estimates of timelines

Estimates of development time vary but not as much as the cost and attrition rates.

[1] The prime-boost NIH-led HIV/AIDS vaccine trial currently running in Thailand is expected to cost US$119 million.

Table 7. Comparison of timelines

	MMV	TB Alliance (streamlined)	DNDi	IAVI	DiMasi et al.	BCG
	Months	Months	Months	Months	Months	Months
Discovery and pre-clinical	**96**	—	**60**	**30**	**52**	**36**
Phase I	12	19	60	30	12	18
Phase II	12	24			26	18
Phase III	24	36		36–48	34	36–48
Approval	12	6			18	12
Total clinical	**60**	**85**	**60**	**72**	**90**	**84**
Years	5.0	7.1	5	6.0	7.5	7
Total	**156**	—	**120**	**102**	**142**	**126**
Years	13	—	10	8.5	11.8	10.5

Sources: MMV (2003); GATBDD (2001); DNDi (2003); IAVI (2000); DiMasi et al. (2003); BCG.

Estimates of total R&D cost for a product for PD PPPs

We have combined the attrition rates in Table 5 with the cost per project stage set out in Table 6.

In the case of IAVI we combined cost estimates taken from the 2000 Scientific Blueprint with the Struck (1998) vaccine attrition numbers. The results for four PD PPPs (see Table 8) show remarkably consistent estimates of total R&D cost per product, ranging from US$128 million to US$192 million. However, there is enormous variability in the balance of cost as between discovery/pre-clinical and clinical development costs. In addition the IAVI figures must be treated with caution. Phase III trials are assumed to cost US$30 million, which may be low. The Struck attrition rates, based on older vaccines, may also be too low. The BCG's microbicides number is high – more than twice the DiMasi et al. figure. This reflects the assumed low success rates as shown in Table 5.

Overall, we have found enormous variability in the key estimates that would make up a portfolio analysis of a PD PPP, notably in attrition rates and cost-per-phase. Whilst these appear to net out in overall estimates of product development costs for four PPPs, they suggest that great caution must be exercised in estimating PD PPP financial requirements.

Estimating in-kind contributions

In-kind contributions are usually thought of as industry contributions, but in principle others can provide for a PD PPP to have access to goods and services at

Table 8. Comparing overall expected out-of-pocket costs (in US$ millions)

	MMV*	TB Alliance	DNDi	IAVI	DiMasi et al.	BCG
Discovery and pre-clinical	62	43	120	52	121	97
Clinical	66	128	72	118	282	803
Total	128	171	192	170	403	900

* We assume that the probability of success in discovery is equal to one. However, much higher numbers are obtained if we use probabilities found in MMV (2003) for the different stages in discovery.

Sources: MMV (2003); GATBDD (2001); DNDi (2003); IAVI (2000); DiMasi et al. (2003); BCG.

no cost or at a price below market value (such as USAID or the EDCTP funding clinical trials).

Kettler and White (2003), in looking at valuing industry contributions, make a distinction between contracts (where the company is providing specified services) and shared partnerships, which can be thought of as joint ventures that require significant, collaborative work on strategic direction as well as on operational detail. Development/licensing agreements may be of either kind. They give two examples: the TB Alliance/Chiron deal on PA824 as a contract product licensing deal whereby TB Alliance pays a licence fee and funds the pre-clinical and clinical development of the product[1] and an MMV agreement with GSK for 'LAPDAP+Artesunate' as a shared partnership.

For the provision of contracted services the company may be: (a) fully compensated; (b) compensated at below market prices; or (c) not compensated at all. The provision of services at below market value represents an 'in-kind' contribution. Kettler and White note that in-kind contributions of great potential value to PPPs include:

- participation of senior people on boards, scientific committees and project groups;
- involvement of senior people in project management;
- donation of products and licences;
- making available compound libraries and screening facilities; and
- donation and/or discounting of equipment.

Incorporating estimates of in-kind contributions into PD PPP funding requirements is difficult. Perhaps the most important and the most difficult area is product licensing. The announcement by IPM to in-license a microbicide product, TMC120, from Tibotec[2] illustrates the issues well. IPM will finance clinical development and so will not save money at that point. However, it has been given a promising product that has been through phase I trials. It would have cost significant sums of money to have developed a product to that stage. IPM will receive royalties if Tibotec chooses to sell the product in developed country markets. In shared partnerships it may be even more difficult to assess the value of the contribution to the PPP. Moreover, in both licensing and shared development deals the exact arrangements are usually confidential.[3]

In-kind contributions are extremely important, particularly where there is a potential developed country market or where other 'pull' incentives exist that will make a pharmaceutical company willing to undertake pre-clinical and clinical research. However, they are difficult to assess.

Estimating the financing needs of the PD PPPs

We undertook the analysis of PD PPP financing requirements using a number of different approaches.

Building up a 'required' portfolio

We set out above a methodology for developing and costing a portfolio based on the required outputs and likely success rates. However, only two PD PPPs have developed detailed portfolio approaches – MMV and DNDi. Examples of their approaches are shown in Figures 1 and 2. Given the lack of data from the other PD PPPs we did not think it appropriate to devote time to second-guessing these two PD PPPs as part of this exercise. Nor was it possible for us, given the data and time constraints, to develop robust estimates of the portfolio requirements of the other PD PPPs. Such an exercise would only be possible with clarification of PD PPP objectives and an understanding of their expectations on attrition rates, costs per phase and in-kind contributions.

Instead we used three more ad hoc approaches.

Estimating the funding gap

Table 9 shows the PD PPP funding gap.

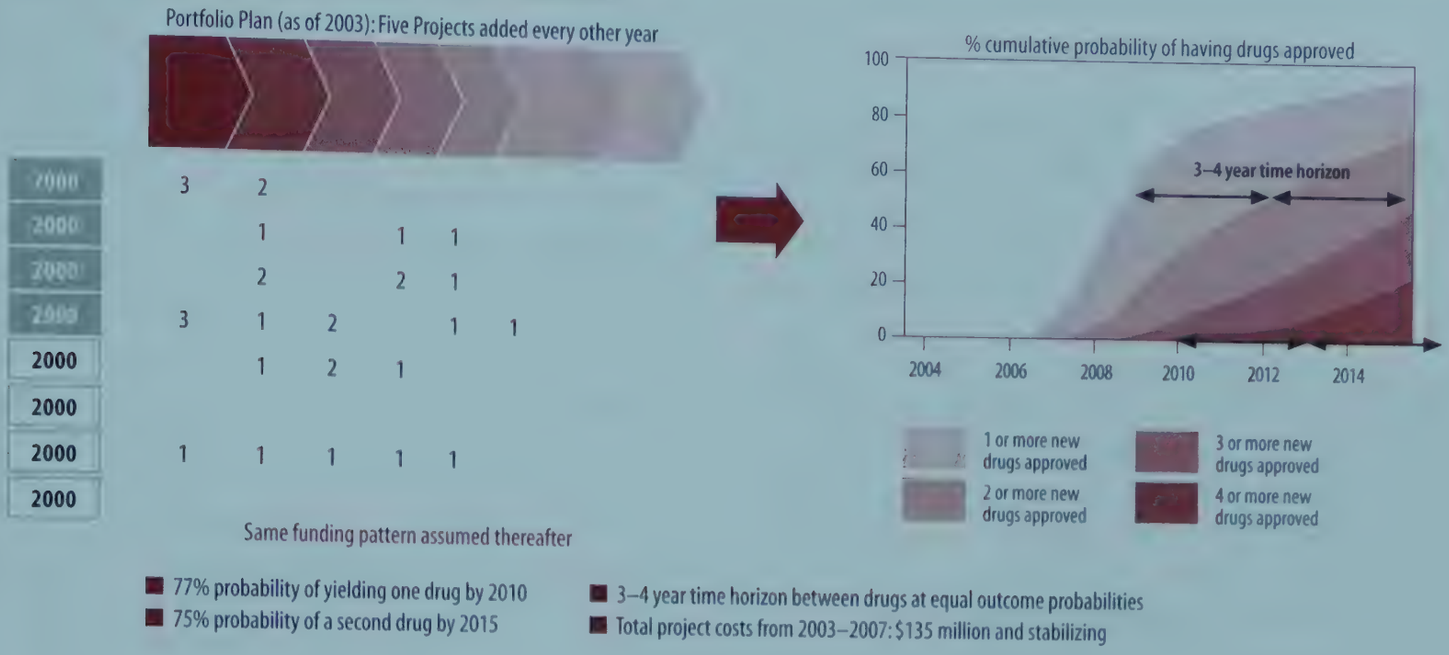
Using PD PPP estimates of the cumulative funding pledges they have received and a mix of sources for cumulative resource requirements, we found for the four PD PPPs we have been looking at plus IPM, a gap of around US$2 billion over the next four years. If IPM is not included, the gap is around US$1.2 billion.

[1] Chiron retains a 'grant-back' option to make and sell the product in richer countries, in which case it repays the TB Alliance for the development costs.

[2] Tibotec is owned by Johnson & Johnson.

[3] It will often make sense to both parties to keep details confidential to avoid 'spillover effects' into other deals. For a discussion of spillover effects in the context of prices, see Danzon and Towse (2003).

Figure 1. Extract from the MMV Business Plan 2003



- 77% probability of yielding one drug by 2010
- 75% probability of a second drug by 2015
- 3–4 year time horizon between drugs at equal outcome probabilities
- Total project costs from 2003–2007: $135 million and stabilizing

Figure 2. Extract from the DNDi Business Plan 2003: Evolution of the portfolio 2000–2014

	New projects	Projects in portfolio	Registered drugs	Failed projects
2003	5	5	0	0
2004	3	7	0	-1
2005	3	8	1	-2
2006	2	7	3	-3
2007	2	7	3	-4
2008	2	8	4	-5
2009	2	7	5	-7
2010	2	8	5	-8
2011	2	8	6	-9
2012	2	8	6	-11
2013	2	8	7	-12
2014	2	8	7	-14

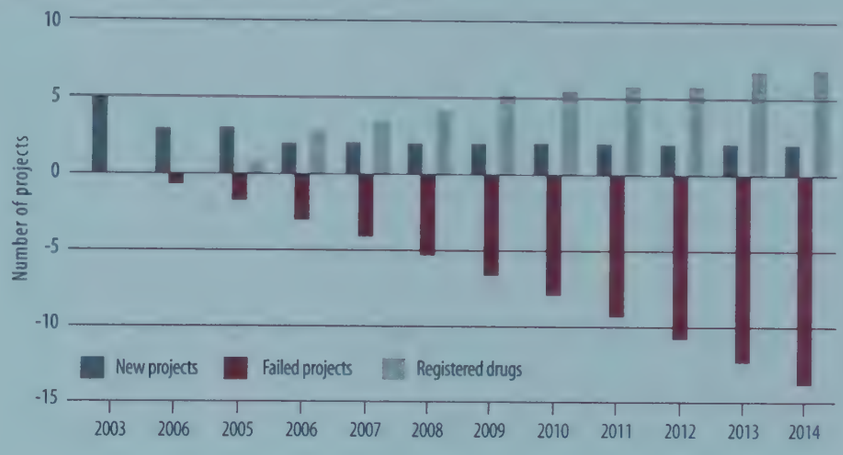


Table 9. PD PPP funding pledges and implied shortfall (in US$ millions)

	Cumulative funding pledged to 2007	PPP estimate of cumulative required resources to 2007	Implied shortfall
IAVI	340	1,036	696
IPM	94.5	775*	680
TB Alliance	42	249	207
DNDi	30	255	225
MMV	97	152	55
Total	**604**	**2,467**	**1,863**

* Of this, BCG estimate that IPM require US$267m in early stage funding and US$508m in late-stage funding.

Sources: IPPPH (based on responses from organizations where received, or from their website, as of early 2004), DNDi (2003); IAVI Scientific Blueprint (2000); BCG; MMV Business Plan 2003–07.

The development costs of the existing portfolio

We looked at the portfolio for the PD PPPs set out in Table 3 and used assumptions about project cost and attrition rates taken from Tables 4–8. We distinguished between drugs and vaccines. For vaccines, we used Struck attrition rates (Struck, 1998) and IAVI mean costs per phase (IAVI, 2000). For drugs, we used DNDi attrition rates and costs per phase (DNDi, 2003). Other possibilities can be used to calculate development costs of the existing portfolio; however, under these assumptions, the numbers came out at US$720m for vaccines and US$730m for drugs, making a total of US$1,450m. It should be borne in mind, however, that the PD PPPs are still building their portfolios.

The costs of bringing a product to licence

A third rule of thumb would be to assume that each of the 14 PD PPPs included in our analysis brought one product to market at an average out-of-pocket cost of US$160m (roughly in the middle of the US$128m–192m range found in Table 8). This would involve costs of US$2.2 billion. We should note of course that some PD PPPs are planning to produce variations of existing products (such as fixed-dose combinations) which would have much lower costs than full development of a new drug or vaccine, and all PD PPPs are seeking to obtain in-kind contributions. However, this calculation gives an indication of possible funding requirements.

The range of estimated financing needs

The range is between US$1.2 billion for four PD PPPs to US$2.2bn for 14 products, depending on the assumptions made, which include:

- which PD PPPs are included;
- size of portfolio;
- attrition rates and costs; and
- any offsetting contributions in-kind.

Conclusions

- If donors are to achieve new licensed drugs and vaccines for neglected diseases, then they have to deal with the low likely success rates of individual projects. They need to manage their risk relative to the expected gains from successfully tackling these global health problems. The best way to do this is through a portfolio of investments. The question is whether the portfolio approach rests with the donor or with the PD PPPs. Overall we conclude that the PD PPPs are better placed to manage a portfolio of projects.
- Some PD PPPs do not have quantifiable objectives. This will make it harder for donors to assess performance.
- Donors should seek to align funding with objectives. There is no point in establishing quantifiable objectives that are out of line with the funding required to achieve them. In particular, if the portfolio is too small relative to the objective because of a lack of funding, then there will be pressure on the PD PPP to keep even unpromising projects going in the hope of achieving their objectives. Having a portfolio that is large enough to deal with project failure is crucial. Conversely there is no point in pushing PD PPPs to hold a portfolio that is larger than justified by the scientific merit of the projects available. This will simply result in larger failure rates later in the development process.
- The PD PPP estimates of discovery and development costs and project attrition rates show major differences in both the discovery/pre-clinical and the clinical phases. Whilst we would expect these to vary by disease area, and to be different for vaccines as compared to pharmaceuticals, it is not clear why there is such variation. There would be benefit in some shared understanding between donors and PD PPPs as to the basis of project cost projections across different PD PPPs.
- Statistical data on failure and attrition rates are very poor for vaccines. There is a case for work to be done in this area to better inform both PD PPPs and donors about likely success rates for portfolio planning and financing purposes.
- Two important areas of cost need more examination – manufacturing costs and investment in clinical trial infrastructure. Both appear to be more important issues in vaccines, because of greater complexity.
- There is a need for a much better understanding of the potential value of in-kind benefits from industry and others. In the case of industry this will in part be linked to the availability of other 'push' and 'pull' incentives which should provide the commercial incentive to encourage companies to provide

more in-kind benefits when they partner with PD PPPs.

- There appears to be a large gap between the funding available to PD PPPs and the finances they are likely to need to get products to market. Donors and PD PPPs need to improve their understanding of the likely size of the gap and how it might be filled.

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ANNEX 9B

The emerging landscape of public-private partnerships for product development[1]

Alison Sander (Consultant, USA) and Roy Widdus (IPPPH, Switzerland)

Executive summary

Over the past decade more than 25 public-private partnerships have been created to develop products for some of the most urgent public health priorities.[2] These are not-for-profit ventures formed to develop products to combat diseases that predominantly affect populations in low- and middle-income countries.[3] This field has now attracted more than US$1.2 billion and a cadre of top management talent to support a series of targeted efforts to develop specific products for specific diseases.

This paper examines the practices of 17 of these product development public-private partnerships (PD PPPs) to understand what these ventures have in common and to look at the variations in how each PD PPP is approaching its particular mission. Specifically, this paper addresses three key questions:

- What defining characteristics do the 17 PD PPPs share?
- How do these entities differ from one another and what accounts for the variation in how each PD PPP is addressing its mission?
- Are there any early observations about which of these variations matter in terms of helping a PD PPP to reach its stated goals?

This is an opportune time to ask these questions. Developing a new drug or vaccine is a challenging and expensive process that can take 8–15 years and requires hundreds of million dollars for a single product. Although many of the PD PPPs considered here are less than three years old and have just embarked on the long, complex research and development process, others, such as the International AIDS Vaccine Initiative (IAVI), have been working to develop an HIV/AIDS vaccine since 1996. Comparing practices and approaches across the 17 PD PPPs can help us see where practices converge, understand the areas where entities are pursing different strategies, and discover whether there are any initial hypotheses on practices that are likely to increase the success of these ventures both individually and collectively.

It is also an important time to look at the emerging 'field' of PD PPPs. Although to date donors have committed an impressive sum (at least US$1.2 billion) and there are many signs of progress, substantial additional resources will be required if this field is going to lead to the development of multiple products. The PD PPP field itself may need to move from a series of individual donors backing individual projects to more of a portfolio approach in which donors collectively look at the sums that will be required for success, at the areas where new donors or expertise will be required, and at the

[1] We would like to express our appreciation for the research contributions provided by Sandra Botta and Katie Storey and for the assistance provided by each of the 17 PD PPPs covered in this paper. The article is the sole responsibility of the authors. Any comments are welcome to Sanderalison@aol.com or roy.widdus@ippph.org

[2] These 25 are listed within the 100 or so PPPs on developing country health problems identified by the Initiative on Public-Private Partnerships for Health (IPPPH). See the Partnerships database at www.ippph.org.

[3] For convenience, these ventures are termed product development public-private partnerships (PD PPPs) and their targets are referred to as 'neglected diseases'. It is worth noting that while very few individuals favour the term 'public-private partnership' because it is so general, no better alternative has been found. In this paper the term 'public' includes the government, multilateral institutions and public academic institutions. The term 'private' includes for-profit businesses (including but not limited to pharmaceutical and biotech companies), private for-profit laboratories and the not-for-profit foundations established by the major pharmaceutical companies. A separate category is used for donors, foundations and not-for-profit entities.

areas where it may make sense to share platforms or expertise across initiatives.

This paper is intended as a first attempt to establish some shared frameworks and terminology in this important field. Product development has been described as both an art and a science. It is as important to understand at an early phase not only what is known in product development for neglected diseases but also to ask what is not known. The authors hope that as the field evolves, future versions of this paper can capture the progress and obstacles in individual PD PPP approaches as well as at the collective level.

Defining characteristics of PD PPPs

At their core, the 17 PD PPPs covered in this paper share five defining characteristics:

- They use some private sector approaches to attack research and development challenges.
- They target one or more 'neglected diseases'.
- They use or intend to use variants of the portfolio management approach.
- Their primary objective is public health rather than a commercial goal.
- They are focused on developing products specifically suited for use in developing countries.

Variation among PD PPPs

Beyond these characteristics, substantial variation exists among the PD PPPs. This variation is examined in four broad areas: strategic variation; financial variation; variation in contributions and roles of the public and private sectors; and operational variation. Some of this variation follows from the mission that each PD PPP has taken on. PD PPPs make initial core choices of which disease to tackle and which product to develop. Once these choices have been made, each PD PPP finds itself in a specific landscape where the private sector is or isn't present, where there is or is not a downstream distribution system, where there are or are not late stage compounds to test and so on. So, for example, the challenges facing ventures such as Areas, which is trying to develop a TB vaccine, are likely to be different from those facing DNDi, which is working on finding a drug for Chagas disease.

Some of the variation comes from strategic choices made about how to partner, with whom to partner, how much to outsource, how much to build in downstream considerations and the like. These strategic and operational choices include the scope of activities to pursue, the approach to partnering, the mix of expertise sought, the way the portfolio is created and managed, and the role of external oversight bodies in monitoring the process. For example, the breadth and scope of activity undertaken along the research-development-access continuum is a key strategic choice. Specifically, advocacy and education are considered core activities for many of the PD PPPs but not all. All PD PPPs undertake communications advocacy to mobilize resources for their own programme of work, but a few PD PPPs have undertaken a more extensive advocacy agenda devoting significant resources and dedicated staff of up to ten employees to these activities. Some PD PPPs see access and distribution as a downstream issue to be explored once a product is developed, while other PD PPPs believe this is a critical area for focus from the beginning.

Most PD PPPs are set up as virtual R&D enterprises and hence make extensive use of contracting, which brings its own challenges.[1] For each type of variation considered, the goal is to identify the common practice or norm (if one has been established) and to show the range of difference around the norm. There is not yet an established methodology for describing the parameters on which PD PPPs can be compared, but this paper examines the following areas of variation.

Strategic variations

- Product/disease target focus.
- Scope of activity along the research-development-access continuum.
- Independent versus 'hosted' legal status.

[1] A risk with a virtual R&D/contract model is that contractors may not have an incentive to spot early problems in their research. Also, there may not be anyone asking the integrating questions across the various steps. Coordinating whether the product could be manufactured at a reasonable price, whether the regulators would approve such a product, whether and how the financing will be available to procure such a product all require advanced coordination and project management skills of a very complex process that may be happening at different times for different candidates.

Financial variations

- Degree to which functions are done in-house or contracted out.
- Size of committed funding.
- Donor base, breadth and duration.

Sector roles and contributions

- Engagement and partnering with business sector, particularly pharmaceutical firms and/or biotechnology companies.
- Engagement with full range of public sector collaborators.
- Mix of expertise.
- Value of in-kind contributions and nature of contributions.

Operational variations

- Portfolio development and management approach.
- Degree of adoption of business-like practices as measured by published materials.
- Governance and accountability mechanisms.

Early hypothesis on variations that matter

Strategic and operational choices can influence both the cost to achieve a mission and the likelihood of success. It is too early to judge what paths will work best, but it is not too early to share a sense of some of the best practices that have emerged. The individuals interviewed for this paper include representatives from each PD PPP and from three of the largest donors funding the field. Donors are quick to state that there is no single formula for success. Individual missions require unique combinations and approaches to pull together the expertise and resources, and to craft the strategy required to develop a product. There are a number of conditions, however, that those donors interviewed point to as important to increase the chance of success. They are:

- A clearly defined mission with a well articulated goal (e.g., new malaria drug by 2010).
- Adequate financing for the initial phases of mission and projection of total financing required to meet the end goal.
- A top management team with access to the best science and a track record in product development.
- A plan that clearly identifies the steps to be taken, by whom and when.
- Active and independent oversight from an experienced board.
- A partnering strategy that includes real collaboration from partners who have the expertise required.
- A robust portfolio with rigorous portfolio management processes.

Donors who were interviewed for this paper affirm that the indicators they look to in measuring the progress for a PD PPP are: a top management team; an active independent board; an active partnering strategy with strong partners; and a robust portfolio.

A partnering strategy requires obtaining access to the expertise required to move through the long and expensive product development process and to develop a product that will work in the setting for which it is intended. Today, much of the upstream and development expertise lies in the private sector where large pharmaceutical companies and some biotech companies have track records of navigating the process from lead candidates, through clinical trials to product registration.[1] Much of the downstream expertise resides in clinicians and national health authorities, who understand the circumstances in which individuals with target diseases present themselves and the settings in which prevention, diagnosis or treatment need to occur. Ultimately, to develop products that work in these settings (e.g., for upstream solutions that will work on the downstream end) will require partnering with a range of different types of participants.

Portfolio management is critical because product development is such a risky and lengthy process. First, a diversified portfolio increases the chance of success by reducing the reliance on a small number of candidates with similar characteristics. Second, robust portfolio-management processes are required to ensure that candidates that do not meet the desired specifications or clinical trial hurdles are actively weeded out, allowing money to be invested in other candidates and different approaches. Evidence of active pruning is one of the signs that gives donors a sense of confidence that portfolio management techniques are being used.

The paper also discusses three tensions that will be different in each PD PPP but that are important to

[1] Beyond the simple question of with whom to partner is the harder question of how to involve partners. Should partners be given IP rights, paid for their services or asked for broad versus targeted support?

manage. First, each PD PPP needs to find the right balance between a focus on upstream science and downstream access issues. A second area that is challenging in any virtual R&D process, particularly if there are separate contracts with different organizations, is managing the multiple interface points. These include places where hand-offs are expected or where different contractors are involved. At a high level, the interface points include the clinical trial sites, the research labs, the procurement and distribution ends, manufacturing and regulatory approval. A third tension to manage is to have the long-term agreements that are needed for intellectual property (IP) issues and for regulatory approval but that ensure adequate flexibility with contractors during the development phase.[1] Some of the older PD PPPs, which have entered into collaborations with larger pharmaceutical companies, now have broad agreements rather than project-specific terms to create flexible terms of collaboration rather than ones tied to a specific compound.

Conclusion

Although PD PPPs have not produced any new licensed product yet, there are many early positive signs. These include both direct and indirect measures, such as:

- Direct fund raising success.
- Early pipeline successes.
- New attention to some neglected diseases by some major pharmaceutical companies and selected biotechnology firms.
- Early advocacy and education successes.
- Development of some infrastructure including clinical trial networks.
- New collaborations between the North and South and some emphasis on capacity building.
- Development of a cadre of management talent, able and willing to apply private sector models to public sector neglected-disease challenges.

It is clear from the levels of public and private funding, the number of products being tested, the trials being conducted and other indicators that much progress has been made. Yet, there are signs that more support is needed if the field is going to bear fruit. As the PD PPP field moves from an initial start-up period into operations, both PD PPPs and donors may want to think about the following four issues:

- How should the PD PPP field be defined – how do we build a shared definition about what we are tracking?
- What resources are required to support and sustain the field and how can the donor pool be expanded?
- What expertise is required from key sectors, and should specific sectors be targeted for increased participation?
- Are there places where greater coordination could improve the chances of success?

In addition there are several factors that are not at present calculated by PD PPPs in a consistent form, but that could be helpful in attracting new donors to the field and in evaluating the potential for success if they were tracked or reported on a consistent basis. These include:

- Potential public health impact if the product is developed.
- Maturity of the science and degree of scientific challenge.
- Existence of demand for a product from clinicians and national health officials.
- Existence (or lack) of efficient downstream country-level distribution systems to ensure access to anticipated products.
- Level and value of specific in-kind contributions from business/pharmaceutical companies and the public sector.

The conference at Wellcome Trust is an important step towards addressing these questions. Although this paper is ambitious in scope, the authors hope it will offer a framework to orient newcomers to the field and to raise some useful questions for long-time supporters.

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The PD PPP field

Product development public-private partnerships (PD PPPs) appeared in the 1990s. They arose in response to a clear challenge. Most of the extant expertise in drug, vaccine and diagnostic development was in the for-profit private sector, but because there was no fi-

[1] This tension can be handled by good IP and legal advisers. For example, it is important to write into any contract agreement that if a candidate does not work or if the PD PPP decides to drop it for portfolio reasons, the research costs can stop.

nancial incentive to develop products for diseases afflicting primarily those in low-income countries, no new drugs or vaccines for some of humanity's greatest scourges had been developed.[1]

Public-private partnerships (PPPs) arose out of a desire to create innovative and effective approaches to some of the leading global disease challenges by harnessing the expertise and knowledge of both the private and the public sectors. In the last ten years, almost 100 PPPs involving the health sector have been formed to address various aspects of neglected diseases.[2] Of these, less than 25 have directly taken on the research and development challenge and focused on product development.[3] This paper looks at the current state of a selection of these PD PPP efforts. We start with what PD PPPs have in common, then explore the many variants that have emerged and finally examine what can be concluded at this point in a longer-term experiment.

Table 1. PD PPP endeavour addresses some of the top global killers

Disease	No. of people killed annually by disease	Number new cases annually	PDPPP	Focus	Committed dollars raised to date
HIV/AIDS	2.8 million	5.5 million	IAVI	Vaccines	$350 million
			SAAVI	Vaccines	$45 million
			IPM	Microbicides	$95 million
			MDP	Microbicides	$27 million
			GMP	Microbicides	$64 million
TB	1.6 million	8.0 million	TB Alliance	Drugs	$42 million
			Aeras	Vaccines	$108 million
			Find	Diagnostics	$30 million
Malaria	1.2 million	300–500 million	MVI	Vaccines	$150 million
			EMVI	Vaccines	$18 million
			MMV	Drugs	$107 million
Dengue fever	19 000	20 million	PDVI	Vaccines	$56 million
Hookworm	3 000	N/A	HHVI	Vaccines	$20 million
Leishmaniasis	51 000	1–1.5 million	DNDi/IOWH	Drugs	$11 million (IOWH)
Chagas	14 000	16–18 million	DNDi/IOWH	Drugs	$30 million (DNDi)
Other			RotaADIP/ PneumoADIP	Vaccines	$60 million
Total	**5.7 million**	**351–553 million**			**$1.2 billion**

Source: Health data: WHO 2002; economic data: survey of PD PPPs for this paper, as of early 2003.

An innovative model

PD PPPs offer a model to address the need for new or improved products to combat diseases of the poor for which prevention or treatment is lacking or inadequate or that have become resistant to current treatments. These neglected diseases include HIV/AIDS, tuberculosis, malaria and other tropical and poverty-related diseases. The 17 PD PPPs covered in this paper collectively represent more than US$1.2 billion in committed funding, cover more than half of the top ten global neglected diseases, and are attempting to produce a full array of tools from prevention (vaccines and microbicides), to diagnostics, to treatment (drugs).

PD PPPs emerged to fill gaps which other organizations could not or would not meet. Their activities nest within a complex web of funders, local public health clinics, national regulatory bodies, international public health standard-setting bodies, advocacy groups and researchers. Each PD PPP must work with myriad other upstream and downstream actors to tackle a given challenge.

The success of a PD PPP will depend on its scope, the maturity of science, the ability to secure funding for its mission and the ability to work with other players in a way that ensures that the right product is de-

[1] Tuberculosis, for example, which kills more than 1 million people a year, was still treated with drugs developed more than 25 years ago that require six months and four drugs in combination to work, and it is still being diagnosed using a technology developed in the 1800s.

[2] Neglected diseases are defined as diseases that predominantly affect the populations of low- and middle-income countries. There are approaches that are not covered in this paper to treating these diseases, such as insecticides for malaria or condoms to prevent transmission of HIV/AIDS. It is also important to recognize that product development is not an end in itself but is a critical step in the process by which scientific knowledge from basic research is eventually applied to benefit health, through the distribution and ultimate use of products by targeted populations.

[3] The rest of the PPPs in the health field address a range of related issues including advocacy, downstream access challenges, education and distribution of existing products.

veloped and that it gets to those who need it most. The variables that many funders look at are the scope of activities undertaken, the potential for impact, the state of the science, and the likelihood of success.

PD PPPs are described as a hybrid model because they must tap product development expertise of the private sector to achieve a social goal. These are often ambitious undertakings in the sense that, although many private sector companies are working on this area, no one has yet developed, for example, an AIDs vaccine. The mission includes upstream challenges in terms of the basic science, funding testing and modifying a lead candidate. If successful on the upstream side, there are then downstream challenges of registering the product, manufacturing it at a cost-effective price and finding a way to get it to people who may live in remote rural areas with little infrastructure.

When undertaken in the private sector, this process from basic science to distribution can cost more than US$600 million and take at least 8–12 years for a new drug. The expectation is that the process would be possible at lower cost and take less time for a neglected disease but we lack good data on this.

Since part of the PD PPP model is an attempt to recreate the advantages of the private sector's successful research model – both the scale advantages of big pharma and the agility advantages of biotech – it is worth elucidating what those sources of advantages are. Both large pharmaceutical companies with extensive R&D track records and smaller biotech companies have developed three areas of advantage: 1) employees with track records and well-honed capabilities; 2) infrastructure incorporating the latest technologies; and 3) processes designed to keep all parts focused on efficiency, profitable product creation and rapid weeding out of non-performing products. Although large pharmaceutical firms are increasingly beginning to contract out services, most still have integrated value chains for product development that ensure that products being developed run the full gauntlet of checks and tests.

A shared portfolio approach to the R&D challenge

The 17 PD PPPs discussed in this paper share five defining characteristics:

- They use some private sector approaches to attack research and development challenges.
- They target one or more 'neglected diseases'.
- They use or intend to use variants of the portfolio management approach.
- Their primary objective is public health, rather than a commercial, goal.
- They are focused on developing products specifically suited for use in developing countries.

Wide variation on other dimensions

Although all these organizations have a fundamentally similar goal – ensuring development of successful

Table 2. PD PPPs described in terms of four key areas of variation

STRATEGIC MODEL			
FOCUS	TARGET DISEASE	SCOPE	AFFILIATIONS
Drugs Diagnostics Other products Vaccines	Multiple Hookworm Dengue Malaria TB HIV/AIDS Other	Basic research Development Access Advocacy	Hosted Independent

FINANCIAL MODEL			
APPROACH	SIZE	DONOR BASE	COMMITMENTS
Subcontract-all Virtual R&D Sub-contract pieces Fully-integrated	$10m $50m $100m $150m $200m $300m	Sole-sourced Multiple Broad-based	One-time Single-year Multi-year

SECTOR ROLES/CONTRIBUTION			
CONTRIBUTORS	TYPE CONTRIBUTION	MIX EXPERTISE	VALUE IN-KIND
NGOs Government Biotech Pharmaceutical	Expertise Board participation In-kind Products Dollars	100% public Largely public 50-50 mix Largely private 100% private	$0 $10m $15m $25m $50m

OPERATIONS MODEL			
BUSINESS MODEL	PORTFOLIO CONTRIBUTION	PORTFOLIO DEVELOPMENT DECISION BODY	EXTERNAL ACCOUNTABILITY/ GOVERNANCE
Business plans Scientific-blueprint Pharmaco-economic report Advocacy roadmap Access plan	Arms length Licensed in-house Largely in-house All developed in-house	Teams Portfolio committee Scientific advisory committee All	Independent Board of Directors Independent stakeholder association Independent clinical trials oversight

Source: Author interviews with individual PD PPPs.

product(s) – they differ on a number of parameters. Some variations follow from the core choices in disease and product. Other variations, such the breadth of activities, use of other parties, and degree of independence or affiliation, follow from the strategic approaches chosen.

Differences in approach

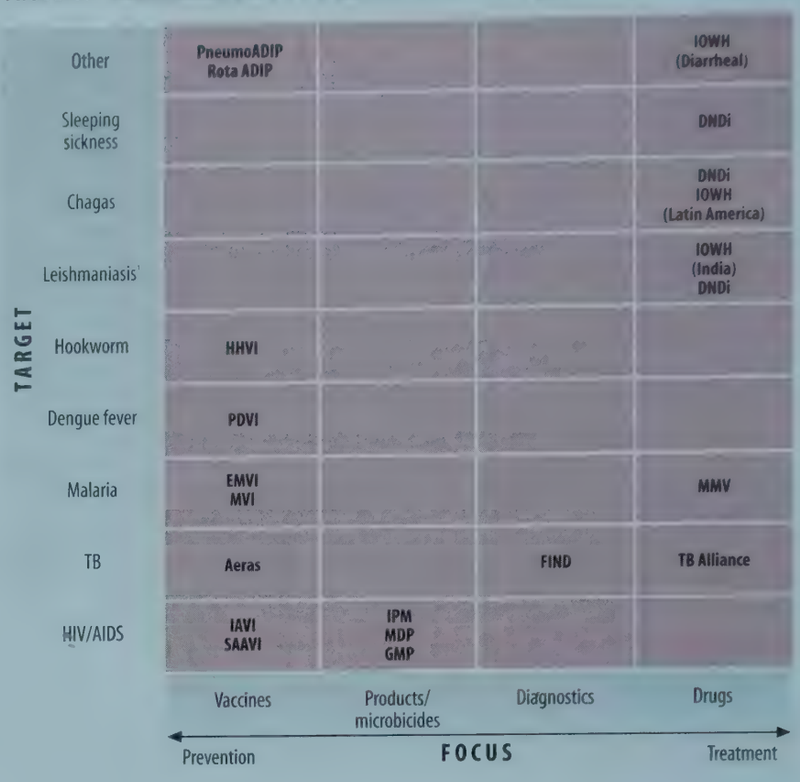
The next section discusses implications of variation for the extent of financing required and for the likelihood of success. This section focuses on four categories of variation: strategic variation, financial variation, sector-role variation, and operating-role variation.

Some of this variation follows from design choices, some from the timing, mission, and state of play in each PD PPP. The earlier PD PPPs have had more time to develop their portfolio management techniques, to develop a broader donor base, and to develop a full set of partners. More than half of the 17 PD PPPs have been in existence for less than four years, and so are just beginning to develop a range of products. They have not yet had a chance to move into downstream activities or to build a robust portfolio.

Each PD PPP has chosen to address one or more disease(s) and one or more type of product(s) (drug, vaccine, diagnostic or other). This choice affects the complexity of its mission in terms of the maturity of the science required, the presence or absence of collaborators, the infrastructure available to help with distribution, the cost to achieve the goal and the ultimate size of the benefit if the goal is achieved. Table 4 below shows that many of the PD PPPs have chosen to focus on the top three killers among neglected diseases: HIV/AIDS, TB, and malaria. Although drugs and vaccines are the most common products being worked on, one PD PPP is focused on developing TB diagnostics (FIND), while three others (IPM, MDP, GMP) are focused on developing microbicide products to prevent transmission primarily of HIV/AIDS.

The challenge undertaken in terms of disease and products affects how many potential partners there are. For HIV/AIDS, because of the prevalence of the disease in many wealthy countries, there are a number of private sector companies competing to develop an AIDS vaccine. For diseases that afflict only people in the poorest countries, it may be very difficult to find any private sector company in the developed world interested in partnering. For diseases such as TB, which have been on the public health radar screen for years, there are extensive compliance regimes and distribution systems in many developing countries, so it may be easier to distribute any drugs developed.[1] For products like microbicides, which are novel and do not match traditional approaches, there may be no existing distribution system on which to 'piggyback'.

Table 4. Seventeen PD PPPs cover a broad range of diseases and foci



[1] Cutaneous and visceral

Source: PD PPP interviews and summary sheets in Appendix.

Table 3. Timeline for development of PD PPPs

1997	1998	1999	2000	2001	2002	2003
IAVI TDR/ Precursor to FIND	Sequella/ Aeras	EMVI	MMV MVI SAAVI	TB Alliance HHVI IOWH GMP	MDP	IPM PDVI	DNDi FIND Rota-ADIP Pneumo- ADIP

Source: PD PPP interviews and summary sheets in Appendix.

[1] WHO has a DOTS (directly observed therapy, short-course) surveillance programme for distributing TB drugs and monitoring compliance in more than 180 countries.

Strategic variations

Disease target and product focus

Deciding which disease to target and what type of product to develop is the starting point for any PD PPP. The rationale for the selection varies from tackling the disease with the greatest mortality and hence the potential for the greatest impact, to tackling the disease and product where the science is most advanced, boosting the probability of success. Some of the diseases chosen, such as HIV/AIDS, are the focus of many organizations; others, such as Chagas disease and leishmaniasis, have received very little attention and may be considered as the most neglected. There are also a few PD PPPs whose mission is to target several diseases (e.g., DNDi seeking drugs for malaria, leishmaniasis and Chagas disease). In the case of IOWH, their aim is to develop vaccines or drugs for multiple diseases (Chagas disease, leishmaniasis, malaria and diarrhoeal diseases).

Independent versus hosted

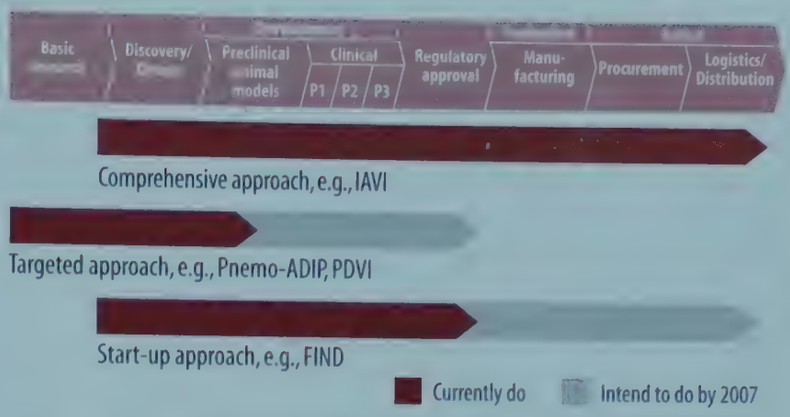
In many cases, the next decision the founders of a PD PPP make is whether to operate independently (which is the case for eight of the 17 PD PPPs considered here) or whether to be hosted in an organization. Some donors have strong views about whether independent or hosted initiatives are more likely to succeed (*see* Table 11 on selected donor views), whereas others see the decision purely on a case-by-case basis, favouring affiliation where there is existing infrastructure and science and favouring independence where there is a need to work with many separate research entities. If the initiative is going to be hosted, key decisions need to be made about where the PPP will be housed and what the terms of the hosting arrangement will be.

Table 5. PD PPPs: independent or hosted entities

Independent	Hosted (Host)
IAVI	SAAVI (MRC-RSA)
FIND	TBDI (WHO/TDR)
Aeras	EMVI (Centre for International Health, Bergen University, Norway)
MMV	MVI (PATH)
IOWH	HHVI (Sabin Vaccine Insitute)
TB Alliance	PDVI (International Vaccine Institute)
IPM	MDP (Imperial College Science Technology & Medicine)
DNDi	GMP (CONRAD)
	Rota–ADIP (PATH)
	Pneumo–ADIP (Johns Hopkins Bloomberg School of Public Health)

Source: IPPPH Partnership Database – www.ippph.org.

Table 6. PD PPPs: variation by activity focus for sample approaches



Source: Author interviews with PD PPPs and summary sheets in Appendix.

Breadth and scope of activity along the research-development-access continuum

This dimension captures information about which activities in the continuum from basic research to downstream distribution PD PPPs are now doing and which activities they plan to do in the future. Table 6 shows scope of activity planned for sample PD PPPs in terms of their current and future focus on activities from basic research, discovery, development, and access. Important choices need to be made in terms of approach to a given activity and the emphasis placed upon it. For example, PD PPPs vary in their methods of pursuing strategies on access and advocacy and even what is understood, or meant by each term differs across entities.

In general most of the PD PPPs focus on early-stage discovery and candidate development. About half currently concentrate on downstream access issues and the other half see this as one of their future priorities. None of the PD PPPs have yet reached the point where full-scale manufacturing is part of their current focus. Research, discovery and development are the upstream and mid-stream parts of the process. Approaches vary more widely in the downstream activities of manufacturing a licensed candidate and distributing it.

Basic research

Basic research is not a priority activity for most PD PPPs. Most basic research takes place in academic or research institutions and the PD PPPs that do engage in it do so through collaboration with these partners. Most PD PPPs engage at the level of discovery and the early stages of translation between basic and applied research. For drug development, this is the stage where biological targets, as well as molecules ('candidates') which are able to act on these targets, are identified.

Discovery/design

Discovery/design is where most of the PD PPPs begin the process, reviewing what is known in terms of the basic science and the need, and beginning to identify lead candidates that have promising characteristics.[1] For each PD PPP, discovery/design is a core activity although there are choices (described in the next section) in terms of how much of this activity is done in-house versus how much is contracted out.

Development and clinical trials

Development typically involves conducting large-scale clinical trials in several parts of the world to test the efficacy of different candidates.[2] This is a step that most, but not all, PD PPPs see as part of their core mandate.

Regulatory approval

Although regulatory approval is already a core activity for most PD PPPs, many see it as a core focus for the future. Any candidate product proven safe and effective in clinical trials needs regulatory approval in each of the countries in which it will be marketed or used. The development process for new pharmaceuticals is geared to generating convincing evidence of product safety and efficacy in the target populations, to standards that will satisfy national regulatory agencies. These may include the United States' FDA or the European Medicines Evaluation Agency, which coordinates applications in the EU, as well as those of disease-endemic countries (DECs). This means trials must be designed meticulously and conducted to Good Clinical Practice (GCP) standards. Meeting these stringent standards has to be built into all the product development activities supported by any PD PPP and means it must have access to specialist expertise in regulatory affairs. They can obtain this expertise by hiring such staff (as has IPM), by contracting for it (as does MMV for some of its projects), or by leaving it to the commercial collaborators to provide (as does MMV for other projects).

Production

Large-scale manufacturing (for amounts beyond those needed for clinical trials) is planned for the future by a number of the PD PPPs. Few if any PD PPPs currently have the facilities to manufacture a licensed compound themselves, but several plan to form licensing agreements with existing manufacturers in developing countries to ensure low-cost versions of the product.

Distribution and access

Distribution and access are also activities where PD PPPs have chosen very different approaches. Some PD PPPs see access as a downstream issue to be dealt with after a product is developed, while others think it is important from early stages. For some PD PPPs, creating a distribution plan is central to their mission while others believe they can hand off their product to an existing distribution system. Access in this sense covers planning for those downstream activities that will influence or facilitate intended beneficiary populations getting the anticipated product, including its affordability. Access issues thus include:

- Assessing, identifying and supporting planning for distribution.
- Developing a product with performance characteristics that are suitable for those environments (pack-

[1] In drug discovery lead compounds are 'optimized', meaning that the compound is manipulated to improve its biological or therapeutic properties. Then compounds are transformed into formulations that can be produced as the dosage forms for use in pre-clinical studies.

[2] Preclinical studies are used to confirm the candidates' biological safety, activity and toxicology profile. If a candidate passes the pre-clinical step then the PD PPP applies to government regulatory authorities for permission for human clinical testing. The clinical trial process is divided into different phases. Using the example from drug development, initial human tests, called Phase I studies, usually involve a small number (20–80) of healthy volunteers and are conducted primarily to assess the safety and tolerability at various dose levels. Phase II studies involve administering the drug to a larger number (50–500) of patients who are diagnosed with the disease being studied to obtain preliminary information on clinical efficacy and determine the optimum dose. Phase III studies are much larger in scale (often several hundred to many thousands of patients) to confirm the safety and effectiveness in the intended patient population.

aging, temperature stability, minimal infrastructure requirements, etc.).
- Anticipating, and in some cases arranging for, financing needed for product procurement.
- Ensuring that there are no unanticipated regulatory hurdles.
- Ensuring access to product manufacturing capacity at a reasonable cost.
- Ensuring adequate health services infrastructure, usually the responsibility of governments.

Addressing access issues creates the need to work with potential collaborators different from those encountered in product development. These may include manufacturers, international institutions such as the World Bank, bilateral aid agencies, developing country disease control programmes, local clinicians who understand the needs and infrastructure available on the ground, local health officials who influence utilization, as well as a host of others.[1] The nature of activities to ensure target population access may differ with product type and the existence and proficiency of 'downstream' actors. For example:

- Children's vaccines enter a reasonably well established distribution system.
- Vaccines for adults or adolescents, or microbicides presently have few downstream actors in place for a 'hand-off'.
- Some products enter reasonably proficient utilization systems (e.g. TB control programmes) whereas in other cases there is little access infrastructure in place (e.g. malaria).

While donors have different perspectives on the right timing and focus that access issues should have in the life of a PD PPP, most agree that PD PPPs need to have examined the relevant access questions and to have identified what actions will be required to ensure anticipated products are put into use without delay. The scientific hurdles in developing a product are half of the battle. Figuring out how these new tools can be deployed in countries facing extreme financial and infrastructure challenges is the other.

Advocacy and education

Advocacy and education activities take place throughout the process rather than at one point in the development cycle. They are considered core activities for many of the PD PPPs, but what activities a PD PPP engages in, how big a staff is dedicated to the task, who they partner with and what they desire to communicate all vary across PD PPPs. All PD PPPs undertake communications advocacy to mobilize resources for their own programme of work.[2] But a number of PD PPPs have undertaken a more extensive advocacy agenda, devoting significant resources and up to ten employees to these activities.

Advocacy and communication activities may be roughly classified as mission related, disease related, or educational communications. Mission-related advocacy includes efforts to promote action by others that will assist the organization to accomplish its mission.[3] Disease related advocacy includes efforts to raise awareness of the need for more attention to a disease/product, not for a specific PD PPP. Examples include the efforts of the TB Alliance, IAVI and DNDi in their respective fields. Educational communications broadly supply information on recent developments to non-specialized audiences. Each of these advocacy efforts can help to move awareness of a whole field forward. PD PPPs vary in the extent to which they take on advocacy and communications activities beyond those for their own resource mobilization (and hence survival); this variation represents true choices on how to allocate resources and on the role that a PD PPP should play.

Implications of strategic choices

Probably the most important decision a PD PPP makes is what mission to take on. The disease and product focus determine the degree of challenge and the ultimate impact if the initiative is successful. The mission affects whether there are other players present with whom to partner, the willingness of donors to fund the enterprise, the basic pattern of epidemiology and

[1] Recent debates in malaria treatment (including LapDap (chlorproguanil/dapsone) and artemisinin-based combination therapies (ACTs)) highlight the need for ensuring such conversations take place early rather than late in the process. See Attaran A et al. 'WHO, The Global Fund, and Medical Malpractice in Malaria Treatment' *The Lancet*; 363:237–40. 2004. This article was followed by the WHO Response to Accusations of Medical Malpractice by RBM/WHO, and the Global Fund to Fight AIDS, TB and Malaria. (See WHO website: www.who.int)

[2] Usually this is limited to potential funders, but in the case of some it includes the general public (e.g. MSF-DNDi).

[3] This category includes the advocacy for international regulatory harmonization and clarification by IAVI, IPM and FIND.

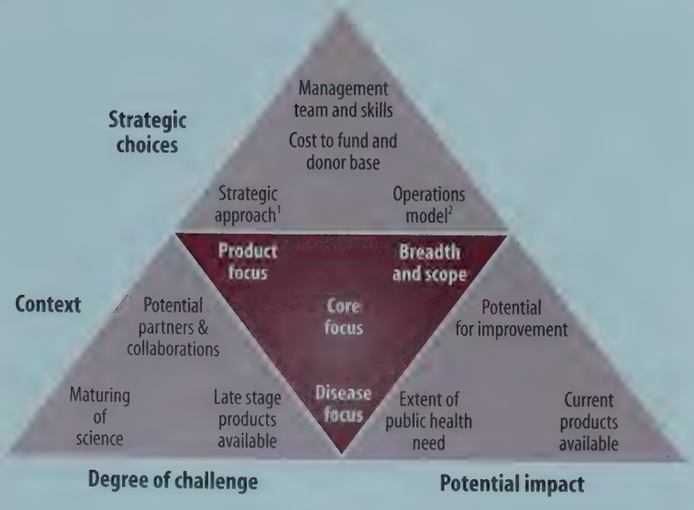
whether there are scientific precedents that need to be improved upon or whether this is an entirely novel enterprise.

For example, PD PPPs committed to work in the field of tuberculosis find a large need, science that has not been improved over many decades, and an extensive implementation and distribution system for TB drugs through the WHO DOTS programme, as well as a system for procuring affordable new drugs through the Global Drug Facility.

PD PPPs focusing on HIV/AIDS work with very active and successful advocacy and education groups and have a number of leading private sector companies working in the same area (since HIV/AIDS is perceived to present an important market opportunity). They therefore have a large number of basic researchers working on both vaccines and drugs. However, in poorer countries no real distribution systems currently exist for public health products like vaccines that are targeted to reach adults and adolescents.

Microbicides represent a completely new class of pharmaceutical products. There is no regulatory precedent for a topical vaginal cream to prevent the spread of sexually transmitted infections. The microbicide-focused PD PPPs (for example, IPM, GMP, and MDP) need to think through new research and regulatory challenges and how the product would be distributed, among other novel first-order questions.

Table 7. Core choices affect context, degree of challenge and potential impact



[1] In-house versus contracted, use of partners, hosted versus independent.
[2] Portfolio development and management, governance model.
Source: A. Sander

There is a key distinction in terms of degree of scientific challenge and level of novelty each PD PPP has chosen to undertake. Some PD PPPs mainly seek to replace products for which there are many precedents. PD PPPs in this category, such as MMV or the TB Alliance, can build on known pathways and processes to achieve their goal. Other PD PPPs are trying to establish the first effective vaccine or drug for a disease for which there is no precedent (e.g., MVI, IAVI, HHVI). And microbicides can be argued to be trying to establish a new class of health products for which only distantly related analogous products exist.

A second key implication from the core choices is the potential for public health impact. Diseases targeted by PD PPPs differ considerably in the size of the populations affected, in terms of age (children versus adults), geographic distribution, health impairment (death, disability, acute, chronic) and socio-economic status of populations affected. While some of these elements include highly subjective value decisions, the PD PPP field might benefit from some thinking around the public health potential from a given mission.[1] Although some donors prefer to work on problems that have the greatest likelihood of success, others prefer the challenges with the greatest potential for impact, even if they are more difficult and riskier. There are no 'right' or 'wrong' areas in the neglected-disease landscape, but it is important to understand the terrain one has chosen and to adapt a strategy to that choice.[2]

Different neglected disease challenges lead to dif-

[1] Some PD PPPs have utilized disease burden or potential public health impact estimates in building a case for their existence and support. However, these efforts have not been systematic or easy to compare. Some methods do exist, albeit not universally accepted, to compare the relative health burdens of disparate diseases. These include the calculation of disability adjusted life years (DALYs) and other measures (QUALYs or quality- adjusted life years, etc.). More difficult is the development of estimates of potential public health impact of envisaged products. This would entail predicting various inputs, e.g. population likely to be reached, usage rates, effectiveness, etc., as well as other variables.

[2] Most funders are willing to embark on a more expensive and more complex task if the payoff is a vaccine that could prevent several million deaths a year. It is beyond the scope of this paper to look at comparisons of impact and risk, but each donor is presumably forming its own portfolio of riskier PD PPPs with higher potential impact and PD PPPs with smaller potential impact but more certainty of success. Different donors may also have different risk profiles and objectives for whether they want to be on a high feasibility versus high impact but riskier endeavour.

ferent strategic choices. What all PD PPPs have in common is the need for strategies that are clearly articulated and that take into account a number of factors. Specifically the strategy for PD PPPs should include:

- A mission for a product with active demand from DECs.
- A mission where the science is sufficiently mature and capable of success if sufficient resources are raised.
- A clearly articulated goal and time frame.
- A scope that leverages rather than duplicates activities already being done by others.

Financial model variation

Approach

In principle, most of the PD PPPs are set up as virtual research and development operations. For most, the goal is to be able to have a lean staff, not to own a lot of infrastructure and to be able to contract or work with the best service providers for each stage of the development process. In reality, however, each step requires a separate decision: will it be done in house, outside but under the careful supervision of in-house staff, or outside and at arm's length? The sum of these decisions influences the amount of financing a PD PPP requires and its balance between control and agility.[1]

Some PD PPPs have chosen to invest in developing their own network of clinical trial sites (e.g., IPM). Others have chosen to work with groups that are developing clinical trial sites, to 'piggyback' on clinical trial sites already developed by their partners (e.g., MMV to a certain extent), or to have an in-house clinical trials expert supervise a series of contracted trial sites.

Although few of the PD PPPs have yet reached the manufacturing stage, this will be another point where similar choices will need to be made. PD PPPs are not likely to own their own manufacturing facilities but will probably contract to a capable manufacturer in the developing world. Advocacy and education are a lower-cost activity and one that many PD PPPs have opted to do in-house although usually in coordination with other outside groups. Almost all the PD PPPs have an advocacy/education director and some have built a whole department around this capacity.

In some cases the approach will be dictated by whether potential partners or contractors are available. In the case of microbicides or of IAVI, which hopes to deliver AIDS vaccines to adults, there may not be an existing delivery structure and greater involvement by the PPP in building a solution may be required. In all cases, decisions on approach, on what needs to be done in-house or outside and whether the work should be closely controlled or fully outsourced need to be made at each point in the value chain on the basis of some combination of cost, criticality, capabilities, flexibility, scale, and availability.

If PD PPPs opt to contract many elements to create a virtual R&D approach, it will be essential to manage the interface points (e.g., the linkages across functions and activities). The risk with many separate contracts is that no one asks the integrating questions. An in-house team will have to work closely with the contractor team to anticipate relevant activity in future stages, build in agility and the ability to update and/or prune the portfolio, and to ensure that there are enough people with incentives to ask challenging questions. Without this active oversight, the risk is that contractors, who may have an incentive to see a stream of work involved in a project continue, may not ask the type of tough or integrative questions that they would ask if the process were in-house.

Size of the entity

There are a number of ways to measure size. One can use committed funds (but this tends to favour the PD PPPs that have been around longer), annual budget, number of professional employees or another indicator. As of early 2004 the 17 PD PPPs included in this study have committed funds ranging from US$10 million to US$350 million. The key factor is not size itself but whether the funds raised are enough to meet the mission selected. Larger or better-funded PD PPPs can support a bigger portfolio, have more in-house expertise, and afford to take on more steps. Those that

[1] Owning the infrastructure or having the expertise in-house has advantages in terms of control but can be quite expensive and may not make sense if the expertise exists in many places already. Contracting can give a PD PPP flexibility in terms of choice of partner and can be a way to lower infrastructure costs, but can leave the PD PPP with less control, depending on how the agreement is written. There can also be risks in contracting that make it harder for a PD PPP to change course later on. Where activities are left (without written agreement) to unpaid collaborators, for example in the plan to 'hand-off' downstream activities to other organizations, the PD PPP can be at risk if these players do not perform adequately.

Table 8. PD PPP funding sources

DISEASE/PRODUCT	PD PPPs																
	HIV/AIDS Vaccines		HIV/AIDS Microbicides			Malaria Drugs	Malaria Vaccines		TB Drugs	TB Vaccines	TB/Other Diagnostics	Other "Neglected Diseases"					
FUNDERS	IAVI	SAAVI	IPM	GMP/ CONRAD	MDP	MMV	MVI	EMVI	TB Alliance	AERAS	FIND	DNDi	IOWH	PDVI	HHVI	Rota ADIP	Pneumo ADIP
FOUNDATIONS																	
Bill & Melinda Gates Foundation	+		+	+		+	+		+	+	+		+	+	+	+	+
Ellison Medical Foundation														+			
Rockefeller Foundation	+		+	+		+			+					+			
The Wellcome Trust						+											
Other foundations	+			+					+				+	+			
GOVERNMENT BILATERAL AID AGENCIES																	
Canadian Government (CIDA)	+																
Government of Denmark (DANIDA)	+		+					+									
Government of the Netherlands	+		+			+		+	+								
Government of Norway	+		+														
Development Cooperation Ireland	+		+					+									
Swiss Government (DEZA/SDC)						+											
Swedish Government (SIDA)	+							+									
U.K. Government (DFID)	+		+		+	+											
USAID	+			+		+	+		+								
OTHER GOVERNMENT FUNDING																	
Government of South Africa		+															
National Institute of Health (NIH), USA		+		+						+			+				
Centers for Disease Control (CDC)				+						+							
MULTILATERAL AGENCIES																	
European Union	+	+						+									
UNDP																	
UNAIDS	+																
UNFPA			+	+													
WHO						+			+			+					
The World Bank	+		+			+											
NGO																	
Médecins Sans Frontières (MSF)												+					
BUSINESS																	
Pharma	+			+									+				
Others	+	+				+							+				
OTHERS																	
	+								+				+				

Source: Responses from PD PPPs to IPPPH survey, where received; in other cases organizations' websites.

are less well funded focus on filling a specific targeted gap and generally try to reduce the need for in-house expertise.

The donor base and duration of commitment

PD PPPs have attracted different donor bases. Half of the PD PPPs exist on funding from a single donor, while the other 50% have three or more donors. In general, having a broad base of funders is thought to increase stability, although a very fragmented donor base, which expects different goals, can present its own challenges. Together, the 17 PD PPPs have attracted funding from more than 60 donors based in more than 15 countries.

Funders for the PD PPPs range from private foundations to governments to NGOs. The type of donor may have an influence on the strategy and approach of the PD PPP. For example, EMVI, the European malaria vaccine initiative funded by EU member states and the European Commission, takes a different approach to that of MVI, which is funded by the Bill & Melinda Gates Foundation. The commitments may come in single-year tranches or be for several years. Multi-year commitments are greatly preferred by PD PPPs because they make planning easier.

Implication of financial choices

Initially, donors were willing to be sole funders for a PD PPP, but increasingly PD PPPs are looking for broad bases of support and for a financial base that matches the ambition of the mission. As the number of PD PPPs grows and as some PD PPPs begin to enter more expensive phases involving clinical trials, the issue of ensuring financial sustainability for individual PD PPPs and for the field as a whole looms larger. Although the universe of donors has grown, that of PD PPPs has grown faster. Initial estimates suggest that substantial amounts will be required over the coming years in order to get over the hurdles required to develop products. Increasingly, donors will look to PD PPPs to see if they have a reasonable financial plan and if they have a clear grasp of the total funding required to meet their life-cycle goal, not just the funds required to get to the next milestone.

There are not necessary right or wrong answers in terms of size and funds required. Different neglected-disease challenges require different financial resources.

What PD PPPs have in common is the need for financial models that take into account the following:

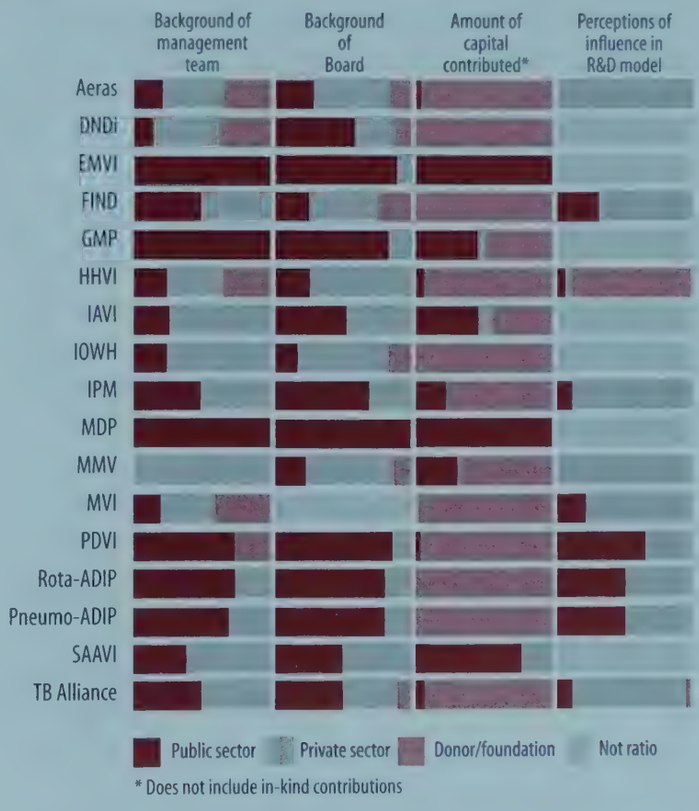
- Financing sufficient to meet initial phases of the mission.
- Financial projections of total life cycle requirement to meet end goal.
- Strong financing base with broad set of funders.
- Funding based on multi-year commitments.

Sector roles and contributions

Another area donors are scrutinizing more closely than in the past is the role that partners, and particularly partners from the private sector, play in a PD PPP and the amount and type of contribution they are planning for the future. The definition of public-private partnership is quite loose and hence includes significant variation. The 17 PD PPPs were asked to rate four items in terms of per cent participation coming from the different sectors: the management team; the board; committed capital; and influences on their research model.

Table 9 shows the range of variation, from PD PPPs with almost no private sector background in their man-

Table 9. Sector participation and contributions



Source: Author interviews of PD PPPs and summary sheets in Appendix.

agement teams and boards to PD PPPs that come predominantly from the private sector.

Nature of contributors

'Contributors' refers to:

- Organizations that provide the capital for PD PPPs.
- Companies and organizations that supply expertise and other in-kind resources.
- NGOs and local community organizations that provide access to local knowledge about how to make a product useful and get it successfully distributed.

On-the-ground expertise in DECs is also beginning to be tracked (e.g., the TB Alliance, DNDi, IAVI and others). Some PD PPPs (e.g., IAVI and the TB Alliance) have stakeholder associations to link to leading global NGOs and to multinational and local organizations in DECs. These groups link to the organizations that have power in the disease control community for their respective product/disease. In some PD PPPs the stakeholder association has a voice in some of the decisions but in others it is only an advisory group.

Type of contribution

There are a number of ways partners and donors can contribute to a PD PPP, and the best-run PD PPPs seem able to increase and expand these relations, obtaining network and positioning advice from their donors, scientific advice from top experts, access to leading infrastructure from their partners, and critical in-country expertise from local health and NGO partners. The types of contribution can be grouped in terms of expertise and talent (which can be in the form of a seconded employee or access to top experts), candidate products (lead compounds, licensing rights for part or all of the world), infrastructure (lab equipment, clinical trial access, manufacturing access, etc.) or on-the-ground access and expertise.

The total financial support for the 17 PD PPPs is more than US$1.2 billion. In-kind support comes from a broader range of collaborators, including pharmaceutical companies, smaller biotech firms, research laboratories and developed and developing country governments and ministries of health. The value of the in-kind contributions is hard to calculate and not yet standardized in spite of several valiant efforts.[1] Less than half of the PD PPPs had an estimate for the value of any in-kind support. The lack of a consistent methodology makes it hard to draw conclusions but the numbers cited for in-kind contributions ranged from less than US$500,000 in two cases to over US$20 million for IAVI and MMV. In MMV's case, reported in-kind contributions were equal to almost 25% of the total capital committed.

Some PD PPPs have much greater private sector participation and in-kind contributions. However, such contributions are easier to obtain when the venture targets a disease area or product that the private sector cares about but is not actively competing in. The PD PPPs that have expanded downstream (e.g., IAVI) have much greater NGO and stakeholder participation. To understand the value of the collaboration it is necessary to distinguish between partnerships where there is only a loose agreement to collaborate (possibly only for a single project) and integral partnerships with many points of collaboration and exchange. An example of an integral partnership would be MMV's agreement with GlaxoSmithKline, which covers multiple research projects and includes collaboration of personnel, candidates and infrastructure over a number of years.

Mix of expertise

The far right column of Table 9 above registers the subjective perception of the mix of influences on a PD PPP's R&D approach. This perception often correlates with the mix of expertise hired. At one extreme, PD PPPs that view themselves as largely copying private sector models may be more likely to push for the greatest rigour ('up-or-out mentality') in managing their portfolios and tend to have a laser focus on the R&D part of the challenge. At the other end, PD PPPs that view themselves as largely public interest (e.g. DNDi) are likely to assign a high priority to building capacity in developing countries and to involve diverse developing country stakeholders. These latter PD PPPs have taken a particularly keen interest in questions of advocacy and access. And PD PPPs that view themselves as part of the hybrid model may see themselves as combining the rigours of private sector portfolio management with access, advocacy, capacity building

[1] Kettler H and White K, May 2003, *Valuing Industry In-Kind Contributions to Public Private Product Development Partnerships*. Initiative on Public-Private Partnerships for Health, Geneva.

and focus on the non-profit world. The PD PPPs that have emerged offer a range of models, which offer different approaches to resolving any public-private tensions.

Implications of sector choices and contributions

Increasingly donors recognize that success in product development depends in part on getting the necessary expertise. This can come from hiring individuals and organizations with track records in product development. It can also be obtained by partnering with an organization with the expertise, infrastructure and processes, or it can be bought (by licensing a later-stage candidate or contract manufacturing).

Each PD PPP has its own challenge and its own mix of organizations that may be interested in collaborating or willing to collaborate, but each needs to be sure that its partnering strategy is maximizing access to the types of expertise required. Similarly, on the downstream side, for PD PPPs with a focus on getting products into the hands of individuals, it is important to focus on getting collaboration from key NGOs, public health officials and local health authorities in the relevant geographical areas. The type of partners required depends on whether the bigger challenge is upstream, midstream, downstream or all of these.

While much of the optimal partnering strategy depends on the challenge selected, there are a few common guidelines:

- Leverage, don't duplicate, existing platforms and knowledge.
- Obtain private sector contributions that reflect real involvement at multiple levels – in management, governance and in-kind contributions.
- Identify a network of scientists and organizations attacking similar problems, position the PD PPP within such a network and learn from similar endeavours.
- Involve stakeholders and individuals in developing countries early rather than late in the process. This is important for all PD PPPs and particularly essential for those with downstream focus.

Operations model

Elements of the business model[1]

Since many PD PPPs use private sector business practices and portfolio management to develop products for neglected diseases, it is useful to look at some sample practices and techniques. Several of the PD PPPs have adopted processes and published materials along the lines of those used by the private sector to plan longer-term strategy. These include developing a business plan, creating a scientific blueprint, doing pharmaco-economics studies, developing an advocacy road map, and in some cases developing an access plan. In reality, all of these are needed as they reflect different parts of the environment a PD PPP must assess and navigate.

Although some PD PPPs, such as IAVI, have drafted each of these documents and made them available on their web sites, that practice is not universal. More than 65% of the 17 PPPs have a comprehensive business plan that describes the strategy and organization structure to meet their mission, spells out the financial requirements for the next five years, and begins to address basic questions about the resources that will be required. Some 41% have developed a pharmaco-economic report, a publication that looks at the market-demand side for a given tool, examines the epidemiology and where the geographic need exists, and includes economic forecasting about the size of this potential market if a product were available.

Of the 17 PD PPPs, 64% have a scientific blueprint. This document examines the state of the science today and develops a plan, often a portfolio plan, for where and how to invest to get to an end product. It usually includes what is and is not yet known in the basic science and a list of those involved in research and development. The PD PPPs that have not published a scientific road map have probably thought about these issues but either have not published a formal plan or have a plan that is for internal use only. Only 29% have an access plan and 18% an advocacy road map.

Although published materials are not the only sign of what business practices are used, they are a good proxy for what issues have been thought through and whether there is a plan that has been jointly agreed to. Gaps in a comprehensive assessment in terms of what is needed to develop and put a product into use may mean the PD PPP is in danger of missing important activities that it or others must do for ultimate success.

[1] As measured by published available materials that address key elements of a PD PPP's strategy – such as a business plan, a scientific blueprint, a pharmaco-economics assessment of the market size, an advocacy road map, and an access plan.

Most of the PD PPPs have established clear milestones and metrics to measure progress toward a long-term goal, but only a few have taken the added step of publishing and sharing these in a way that allows interested parties beyond the board to see the progress.

Portfolio state of development

Beyond the differences in philosophy, business practices and published strategies, there are important differences in whether the PD PPP plans to develop its own portfolio and how robust or diversified the portfolio is intended to be. The PD PPP distinction was originally intended for PPPs that had committed to and embarked on plans to develop a new product using advanced portfolio management techniques of diversification, pruning and risk balancing.

That strict definition is challenging, because some of the PD PPPs intending to develop portfolios have only recently started up and are licensing their first candidates. Others do not plan to form their own robust portfolio of candidates because they are augmenting the efforts of a private sector company that already has a product but has not adapted it to developing world needs. In that case it may not make sense for a PD PPP to develop its own portfolio. The best examples in this category of augmenting private sector efforts are GAVI's two ADIPs (Accelerated Development and Introduction Plans). GAVI has put together a large portfolio of vaccines that have been or could be developed and has chosen to spend US$60 million to see whether the existing pneumococcus vaccine sold by Wyeth and the two vaccines for rotavirus that are close to being marketed could be adapted for the developing world.

Clearly it takes fewer resources and staff to augment or adapt an existing private sector product than to create a whole portfolio of candidates that need to be tested and taken through the full development cycle of clinical trials.

Portfolio characteristics

A number of characteristics indicate how robust a portfolio is. At the highest level, these relate to the size, diversity and quality of the candidates in the portfolio. A portfolio that includes candidates at different stages of development (for example, pre-clinical or phase I, II or III testing) may be considered the most diversified, but creating this advanced state may take considerable time when there are no existing late-stage products. At the next level, the quality of the portfolio is a function of the questions that have or have not been anticipated. Are the potential candidates licensed for the rights and time frame required? Are they easy to manufacture? Are they likely to function in tropical and poorer parts of the world?

A third layer of questions relate to active portfolio management. Does the portfolio have a balance of risky products with greater potential and safer bets with lower potential? Has the portfolio been pruned? Is it meeting its milestones and has it been adjusted for the results from clinical trials? A large portfolio that includes candidates that are not viewed as likely to succeed can waste significant resources and serve as a distraction.

Portfolio management

The majority of PD PPPs operate as virtual R&D managers but they still face a number of choices about portfolio management. These include whether to develop the candidates in-house or to license candidates that others have developed. There are also choices related to the approach: whether to act as a virtual R&D department or to adopt the more robust type of portfolio management exemplified by IAVI, whose 80 employees include experts on each stage of the research problem, including manufacturing experts.

This type of integrated and expensive approach clearly is not appropriate for all of the PD PPPs. For example, PDVI, which is looking for a process to create a pediatric dengue vaccine, faces a different challenge requiring a very different approach to portfolio management. At least one company (Aventis Pasteur) is actively developing a dengue vaccine for adults which is in late-stage clinical trials. PDVI has been charged, not with creating its own products, but rather focusing on whether the existing candidates can be adapted for children.

Depending on the original mission and the level of private sector involvement, projects for the portfolio can be developed in-house, licensed in-house or developed by others at arm's length. The tasks involved in managing the portfolio depend on the scale of the challenge. Only a small staff may be needed, or the PD PPP may require in-house experts who can actively

coordinate and work with others involved at each level of the product development challenge.

Portfolio development approach

Almost all the PD PPPs with active portfolios go through a similar process. There are calls for proposals, evaluations of those proposals, teams to identify the best approaches, and people skilled in licensing to bring in-house the best leads not being developed elsewhere. What differs by PD PPP, depending on the stage of development and the challenge, is the level of focus on portfolio management and the use of external oversight to ensure that the process is carried out efficiently and aggressively. All the PD PPPs with active portfolios have a chief scientific officer whose job requires knowing the science and the best candidates and who is responsible for developing a plan to create and maintain the most robust portfolio and for testing and demonstrating the efficacy of the best lead candidates. The distinctions are found in how this process works in each PD PPP, and how much oversight is provided and by which groups. Many PD PPPs have a portfolio committee, and most of those with active portfolio management have an independent scientific advisory committee (SAC).

The oversight of the process and external review are very important. It is not easy to drop a candidate that has been widely touted and actively supported for years, but this is a critical part of making the portfolio process work efficiently. As one head of a PD PPP explained: "You have not really learned about portfolio management until you have had to drop a favoured candidate from your list." An important check on the portfolio development process is to look at which candidates have been dropped and when, and whether oversight is effective. Portfolio management is not only about creating and collecting the portfolio, it requires active screening and making tough decisions to ensure there is a portfolio of real candidates with potential for success.

Governance/accountability of the venture

How the portfolio is managed is a subset of a set of issues about external oversight for the PD PPP as a whole. Legally independent PD PPPs have boards of directors, although this is more complex for the PD PPPs that are hosted. What differs is who is on the board, how active the board is, how often it meets (ranging from one to five times a year) and whether it serves as a 'rubber stamp' board or asks challenging questions. In some cases donors sit on the board (formally or ex-officio) but in many cases they do not. It is worth asking a series of questions about how effective the board oversight is, including:

- How extensively are board members involved?
- How well do they understand the challenges of portfolio management?
- What type of expertise do they bring to the process?

The board of legally independent PD PPPs must also assume a number of responsibilities; key among them are providing overall risk management, ensuring fiscal accountability and guiding the recruitment of a top management team.[1]

In addition to a board of directors and a scientific advisory committee, some PD PPPs have other oversight committees, such as clinical trials or policy advisory committees. Again, the effectiveness of these groups depends on the expertise of their members, the quality of their contribution and their own sense of accountability. A few PD PPPs have stakeholder associations. In some cases this is just a list of organizations that are working on parallel activities, but in other PD PPPs this is a way to ensure that the population that is ultimately meant to benefit (patients in low-income countries) has a say in the process.

Implications of operating model choices

Each PD PPP has essentially chosen its own operating model within whatever constraints are imposed by the availability of suitable collaborators. While this guide can suggest some important questions to ask and distinctions to make, the validity and likelihood of a given set of operating model choices depends on the mission and end goal of the PD PPP and the amount of financial resources and partners available to meet that goal. Those PD PPPs that are focused on upstream activities and on creating a full portfolio will require an operating model that allows for robust and rigorous processes for selecting and licensing candidates and for taking them through clinical trials and acting quickly

[1] See IPPPH (2004), *Liability and Other Legal Issues for Organizations Engaged in Product Development Through Public-Private Collaboration*, March, Geneva.

on the results. PD PPPs that intend to work with the private sector on an existing private sector formulation may not need to build their own portfolio and may be able to use a leaner team to work on focused clinical trials and downstream issues to be sure that an existing or late-stage product can be adapted for the needs of developing countries. Different neglected-disease challenges require different customized approaches. What all PD PPPs have in common is the need for operating models that take into account the following:

- A top management team with full capabilities required to meet the goal.
- An active and independent board of directors (or oversight committee, if hosted), which represents all key sectors and which demands accountability.
- An active and independent SAC, which represents all key technologies and required expertise.
- Published materials with clear milestones and metrics.
- Robust and rigorous processes for pruning projects and overseeing portfolio development in the larger PD PPPs.

Implications of variations

It is early in the life cycle of PD PPPs to draw any definitive conclusions about which design choices are more likely to lead to the development and use of effective products. However, what can be seen clearly now is that different choices have very strong implications for funding requirements and it is possible to suggest some early hypotheses about which variations may be likely to correlate with success.

Some of the implications of the choices shown above are listed in Table 10.

Table 10. Choices and variations have implications for cost to fund and likelihood of success

STRATEGIC MODEL			
FOCUS	TARGET DISEASE	SCOPE	AFFILIATIONS
Drugs Diagnostics Other products Vaccines	Multiple Hookworm Dengue Malaria TB HIV/AIDS Other	Basic research Development Access Advocacy	Hosted Independent

IMPLICATIONS

Cost to fund, degree of scientific challenge, potential public health impact, likelihood of success

FINANCIAL MODEL			
APPROACH	SIZE	DONOR BASE	COMMITMENTS
Subcontract all Virtual R&D Sub-contract pieces Fully-integrated	$10m $50m $100m $150m $200m $250m $300m	Sole-sourced Multiple Broad-based	One-time Single-year Multi-year

IMPLICATIONS

Cost to fund, expertise available, chance for sustainability, adequacy of funding for the task

SECTOR ROLES/CONTRIBUTION			
CONTRIBUTORS	TYPE CONTRIBUTION	MIX EXPERTISE	VALUE IN-KIND
NGOs Government Biotech Pharmaceutical	Expertise Board participation In-kind Products Dollars	100% public Largely public 50-50 mix Largely private 100% private	$0 $10m $15m $25m $50m

IMPLICATIONS

Expertise and depth of resources available, ratio of public to private sector input

OPERATIONS MODEL			
BUSINESS MODEL	PORTFOLIO CONTRIBUTION	PORTFOLIO DEVELOPMENT DECISION BODY	EXTERNAL ACCOUNTABILITY/ GOVERNANCE
Business plans Scientific-blueprint Pharmaco-economic report Advocacy roadmap Access plan	Arms length Licensed in-house Largely in-house All developed in-house	Teams Portfolio committee Scientific advisory committee All	Independent Board of Directors Independent stakeholder association Independent clinical trials oversight

IMPLICATIONS

Cost to fund, likelihood of developing successful portfolio adequacy of oversight, use of private sector models

Source: Author interviews with PD PPPs.

Implications for funding required

One of the most expensive parts of the product development process is the clinical trials carried out in phase I, II and III testing. These are expensive because of recruitment costs, the labour and time involved, safety requirements and often the multiplicity of test sites. In a number of cases a candidate, which has been tested at phase II level, requires modification and retesting. Therefore, if a candidate exists that has already passed early testing (i.e., a candidate in phase III or later), it can be licensed or modified for use in developing countries, and the funding requirements for the PD PPP will therefore be lower.

If a PD PPP has to build its own infrastructure (laboratory sites, clinical trial sites, or even potentially manufacturing sites) the cost will be much higher than if it can leverage existing facilities. Building facilities rather than contracting for them with others makes sense only where existing facilities are not available or there is a need for greater control.

Some potential implications for the success and sustainability of the venture

It is too early to judge what paths will work best, but some potential pitfalls can already be identified. Table 11 also suggests that donors have their own views, which in many cases pull in different directions, about what choices are important and likely to correlate with success.

All individuals interviewed for this paper agreed that there is no single formula for success and that product development is a complex process even for organizations with billions of dollars and large staffs. That being said, there are several conditions frequently cited as important elements to maximize the chance of success. They are:

- A clearly defined mission with a well articulated goal.
- Adequate financing for the initial phases of mission and projection of total financing required to meet the end goal.

Table 11. Critical success factors mentioned by PD PPPs and selected donors

	MENTIONED BY PPPS	MENTIONED BY DONORS*		
		Donor A	**Donor B**	**Donor C**
Strategic	'PD-PPP should have wherewithal to do everything directly or indirectly with a partner." "For us being independent was important...we need to be very nimble and flexible to do the job."	"We look for places where science is mature and social demand is robust." "We are willing to take risks but also look for low-hanging fruit where we can have strong impact."	You need to be independent in this game to take on the real challenges."	"Look for a venture that is unique and takes a stand."
Financial	"We need long-term commitments but many donors are set up with annual planning cycles."	"We are willing to take risks commensurate with the opportunity." "Size and momentum in terms of a broad base of funders is important."	"I look for that real sense of trust and rapport where they tell me their deepest concerns."	"More funders is important and serves as a kind of risk spreading."
Sector roles	"Tremendous strength and flexibility from ability to be placed between private and public sector." "Nothing succeeds like success... now business wants to be in on deals with us because their competitors are."	"We like a mix of US and European donors." "We look for good leadership with enough understanding of the space that it doesn't matter which sector they come from."	"It is all about people not structure... Hire people and find partners that have a track record."	"Need to expand governance to include the voice of the poor." "I feel strongly there should be private sector participation."
Operating	"Need management structure that enables cold-hearted look at portfolio choices."	"Portfolio and an economic mindset are key."	"No one is successful to date...these are all experiments in process."	"Important to do capacity building in developing countries."

* At least 2–3 interviews per donor.

Source: Author interviews with PD PPPs and funders.

Table 12. Early hypotheses on selected critical success factors

Strategic	• Clear mission for product with active demand from disease-endemic countries • Mission where science is sufficiently mature that success is possible with adequate resources • Clearly articulated goal and time-frame (e.g., new malaria drug by 2010) • Scope which is leverage activities already being done by others and which anticipates downstream access and other important questions
Financial	• Financing sufficient to meet initial phases of mission • Financial projection of total life cycle requirements to meet end goal • Strong financing base with broad set of funders • Funding based on multi-year commitments
Sector roles	• Leverage and link to existing platforms and knowledge • Contributions that reflect real involvement from private sector at multiple levels in management, governance, in-kind contributions • Identification of and positioning within network of scientists and organizations attracting similar or adjacent problems • Involvement of leading stakeholders and clnicians in developing countries early rather than late in process
Operating	• Exceptional management team with full capabilities required to meet goal, that works well together, and that can adapt over life of project • Active board of directors which is independent and demands accountability • Active SAC which represents all key technologies and required expertise • Published material for transparency (e.g., business plan, scientific blueprint, access and advocacy plan if appropriate) with clear milestones and metrics • Robust and rigorous processes for pruning and overseeing portfolio develpment

Source: Author interviews with PD PPPs, funders and industry.

- A top management team with access to the best science and a track record in product development.[1]
- A plan that identifies the steps to be taken, by whom and when, in order to achieve the mission.
- Real collaboration from partners with the expertise required.
- Active and independent oversight from an experienced board.
- A robust portfolio with rigorous portfolio management processes.

In addition to these early hypotheses on questions that are worth asking, there are three tensions, which will be different in each PD PPP but which are important to manage. First, each PD PPP needs to find the right balance between a concern on upstream science and on downstream access issues. Even if there is a vaccine or a new drug therapy, it is important to remember that a lot of other elements will be critical to ensure that they are taken up early and widely. That being said, a new PD PPP can get stretched very quickly if it takes on extensive activities at both ends of the value chain; focus is important.

A second area that is challenging in any virtual R&D process, particularly if there are separate contracts with different organizations, is managing the multiple interface points. These include places where 'hand-offs' are expected or where different contractors are involved. At a high level, the interface points include: clinical trial sites; research labs; procurement and distribution ends; manufacturing; and regulatory approval.

A third tension to manage is to have the long-term agreements for intellectual property and for regulatory approval, but to ensure adequate flexibility with contractors during the development phase. This tension can be handled by good IP and legal advisers but it is important to write into any contract agreement that if a candidate does not work or if the PD PPP decides to drop it for portfolio reasons, the research costs can stop. Some of the larger PD PPPs, which have formed agreements with larger pharmaceutical companies, now

[1] Bringing in individuals at the management team or board level with a product development track record can help reduce the learning curve.

have blanket collaboration terms rather than project-specific terms.

Conclusion

The PD PPP field began as a collection of individual approaches to see whether pharmaceutical industrial knowledge and tools for product development could be applied to neglected diseases. Although there is no new product yet, there are many early signs of success. These include both direct and indirect measures such as:

- Direct fund raising success.
- Early pipeline successes.
- Stimulation and support of a network of players.
- Early advocacy and education successes, which have helped to support new pricing and drug funding mechanisms such as the Global Drug Facility for TB drugs.
- Development of some infrastructure including development of clinical trial networks.
- New collaborations between the North and South and some emphasis on capacity building.
- New attention to some neglected diseases by some major pharmaceutical companies and selected biotechnology firms.
- Development of a cadre of management talent able and committed to applying private sector models to public sector neglected disease challenges.

It is clear from the levels of public and private funding, the number of products being tested, the trials being conducted and other indicators that much progress has been made. Yet, there are signs that more support is needed if the field is going to bear fruit. Ironically, the initial success of the model has led to a proliferation of PPPs for health and PD PPPs. Although this can be read as an initial endorsement, the present set of funders is unlikely to be able to support all of the initiatives being pursued by the current PD PPPs. This suggests a need for financial planning by both PD PPPs and donors to clarify the extent of the likely gap. New and additional funding can be attracted, but that may require a new level of communication and outreach.

It is an important time to look at the 'field' of PD PPPs that is beginning to emerge. The PD PPP field itself may need to move from a series of individual donors backing individual projects to more of a portfolio approach in which donors collectively look at the sums that will be required for success and at the areas where new donors or expertise will be required and where it may make sense to share platforms or expertise across initiatives. As the PD PPP field moves from an initial startup period into operations, both PD PPPs and donors may want to think about some of the following issues.

First, the need to define the PD PPP field. Is it useful to think of vaccine, drug, diagnostic and other product development PPPs together at the same time? Is it useful to group organizations that are augmenting private sector efforts to take an existing product into developing countries with organizations that are trying to develop a new product category, such as microbicides? Is it useful to look at single candidate product development efforts in addition to broader portfolio approaches? There may be good reasons to treat such a broad group as one category if there are useful areas of collaboration or lessons between these different areas. However, doing so also runs the risk of increasing confusion rather than clarifying the field.

Second, as PD PPPs move from an experimental to a more established phase, there is a clear opportunity for greater coordination both within and across PD PPPs to ensure that best practices are shared, money is spent in the most efficient way and the platforms that have been built by one PD PPP and could be shared with others are known and leveraged. Collaboration in specific targeted areas may make sense across donors, within and across diseases and across product areas for a disease. There are a number of informal collaborations and discussions taking place today, but a more systematic approach could be beneficial.

Third, it is important to look at the expertise being called upon and places where gaps still exist. If PD PPPs are going to succeed as a whole, two groups may need to be consistently brought into the discussion: private sector R&D experts and developing country clinicians and stakeholders. The expertise of the commercial pharmaceutical industry is essential, but not necessarily easy to recruit as industry's motivation is largely focused on making a profit. As Table 9 shows, the private sector, which holds much of the knowledge about how to turn basic research into applied research into products, is participating in some PD PPPs but not to any consistent degree. A lone indi-

vidual on a board (particularly if retired) is not enough to transfer expertise.[1] The question of private sector participation, where it has occurred and where it has not, is important and worthy of its own investigation.

Similarly, there is a real potential risk in any R&D process that a good product will be developed but not matched to the needs of the end users. The obstacles to getting a useful product to the end user include, among others, regulatory, procurement, distribution, infrastructure, manufacturing and utilization hurdles. It is important that knowledgeable end users be brought into the process from the relevant locations at the earliest possible time and given an active voice in the process. These conversations also should include regulatory gatekeepers and technical advisors like WHO and National Health Officials who often influence what local health authorities regard as feasible. The scientific hurdles in developing a product are only half of the battle. Figuring out how these new tools can be deployed in countries facing extreme financial and infrastructure challenges is the other.

In closing, it is important to applaud the efforts of the many individuals who have carried the PD PPP field to this point. These include donors, researchers, advocates, pioneers, academics and clinicians. Many who have embarked on this experiment have changed career paths or switched from secure jobs in labs or companies to place themselves on the front lines of an evolving field. The early signs are exciting. Now is the time to define both the field and its requirements to create a powerful array of new tools for combating the greatest killers on the planet.

[1] The issue of ensuring real collaboration of the private sector is often discussed as a problem but is not taken up at a level required to change the dynamic. While some individuals and companies from the private sector have chosen to participate, others find the PD PPP field confusing and state that research is "not being done in a rigorous enough way to succeed". Still others are willing to collaborate but not on terms acceptable to PD PPPs.

APPENDIX

This appendix consists of one-page overviews of each of the 17 product development partnerships around which the 15–16 April 2004 IPPPH meeting was formulated.

These summary sheets were completed by the product development partnerships themselves around the time of the meeting with the aid of the guidance and definitions outlined below:

Guidance and definitions

"These one-page summary sheets are an initial attempt to collect information on the 17 PD PPPs invited to the 15–16 April 2004 gathering at Wellcome Trust. The objective of these sheets is to give participants [and readers] a quick way to understand who is targeting which diseases and products, and how far along they are in their efforts."

Relative contribution

This section is meant to capture the relative expertise and capital that have been contributed by different sectors:

- *Public includes the government, multilateral institutions, public academic institutions, or government labs.*
- *Private includes for-profit businesses (including but not limited to pharma and biotech companies), for profit laboratories, and the not-for-profit foundations established by the major pharmaceutical companies.*
- *Donor or Foundation includes all non-profit and charitable enterprises excluding government donors (who are classified under public) and pharmaceutical foundations (who are included in private to capture activities of the pharmaceutical companies).*
- *The amount of capital contributed counts all funds committed. It should not include in-kind contributions.*
- *The amount of in-kind contribution is an estimate of the in-kind/non-financial contributions that partners have contributed in terms of expertise, infrastructure, and compounds. We count as in-kind contributions those from corporations paid for a service/product at below market value, where this can be documented.*
- *R&D model processes is a subjective rating to capture the influence from each of the sectors on the R&D model employed by the PD PPP.*

Scope of activities

This section compares the scope of current activities and activities planned for the future. For each activity now being done or planned, the question is whether it is done primarily through in-house staff or mostly out-sourced through contracts to a third party, even if generally overseen by in-house staff.

Portfolio strategy

This section asks for the number of products today and forecast for the end of 2005 in the portfolio. It should not include compounds that others in the field are testing for the same disease where there is no support from your organization.

Size/Management

This asks for a summary of the staff size, governance and advisory structures:

- *Total staff excluding secretarial support.*
- *Capital raised to date, excluding in-kind contributions.*
- *Number of donors contributing funds.*
- *Size of various bodies, where relevant.*

Published materials

This examines whether the organization has adopted certain types of business practice through identifying published materials available to the public and donors:

- *A scientific blueprint examines the state of the science today and develops a plan, often a portfolio plan, for where and how to invest to get to an end product. It usually includes what is known and not yet known in the basic science and a list of those involved in research and development.*
- *A business plan describes the strategy and organization structure required to meet a mission. It spells out the financial requirements and begins to address basic questions about the approach required to meet the mission.*
- *A pharmaco-economic report looks at the market demand for a given product, the epidemiology and the geographic areas in which a need exists. It includes economic forecasting about the size of this potential market if a product were available.*
- *An access plan lays out a strategy for how to get the product in the hands of those who need it. It can include a distribution strategy for the relevant areas, patient groups and given the existing health care infrastructure. It can include groups that need to be involved in distribution, and a plan for developing the needed financial mechanisms so the product can be procured, among other issues.*
- *An advocacy/education plan lays out a strategy to increase public awareness and/or change public policy at the key levels. It may involve a study of relevant policy makers, opinions, regulations/legislations, and points of influence among other factors.*

List of in-kind contributors

This section lists anyone providing any 'in-kind' contributions, with their type of contribution and assessment of financial value, where available.

The summary sheets that follow represent the responses of individual PD PPPs as supplied in mid-2004.

Aeras Global TB Vaccine Foundation
Launch date: 1997
Focus: Develop & distribute vaccines
Target: TB
Website: www.aeras.org

Director: Dr. Jerald Sadoff
Address: Aeras Global TB Vaccine Foundation
7500 Georgetown Road, #800
Bethesda, MD 20814
USA

MISSION

The **Aeras Global TB Vaccine Foundation** (formerly known as the Sequella Global Tuberculosis Foundation) was founded in 1997 to help develop new concepts and tools to control the global TB epidemic.

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	9	22	44	33
Background of board	8	28	57	14
Amount of capital contributed	$107.9m	2	—	98
Amount of in-kind contribution (est)	—	—	—	—
R&D model/processes (est)	—	—	100	—

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Research	Y	Y	Y	Y
Pre-clinical	Y	Y	Y	Y
Phase I testing	Y	Y	Y	Y
Phase II testing	Y	Y	Y	Y
Phase III testing	Y	Y	Y	Y
Regulatory approval	Y	Y	Y	xxx
Manufacturing	Y	Y	Y	Y
Distribution/'access'	Y/N	Y/N	Y	Y
Advocacy/education	Y	Y	Y	Y

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts)	6	Forecast end 2005 portfolio (# of pdts):	6
• Pre-clinical:	4	• Pre-clinical:	—
• Phase I:	2	• Phase I:	—
• Phase II:	—	• Phase II:	4
• Phase III:	—	• Phase III:	2
• In-market:	—	• In-market:	—
Number of clinical trials:	—	Number of clinical trials:	10
Location of clinical trials: S. Africa, USA, Europe		Location of clinical trials: S.Africa, USA, Europe	

SIZE/MANAGEMENT

Number of professional employees:	64
Capital raised to date:	$107.9m
Number of donors:	1
Board of Directors size:	7
Scientific Advisory Committee size (if used):	6
Policy Advisory Committee size (if used):	—

PUBLISHED MATERIALS

Use of:	
• Scientific blueprint	Y
• Business plan	Y
• Pharmaco-economic report	Y
• Access plan	Y
• Advocacy plan	N

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value
Bill & Melinda Gates Foundation	$107.9m	
NIH	$20m	
EDCTP (projected)		$20m
US AID (projected)	$25m	
ECE (projected)	$25m	

DNDi
Drugs for Neglected Diseases *initiative*

Drugs for Neglected Diseases Initiative (DNDi)
Launch date: July 2003
Focus: Drug R&D
Target: Sleeping sickness, leishmaniasis & chagas
Website: www.dndi.org

Executive Director: Dr. Bernard Pecoul
Address: 1 Place St. Gervais
Geneva 1201
Switzerland

MISSION

DNDi will improve the health and quality of life for people suffering from neglected diseases by using an alternative model to develop drugs for these diseases and ensuring equitable access to new and field-relevant health tools. It will also build public responsibility and leadership in addressing the needs of these patients. DNDi will achieve its goals by building an R&D project portfolio, raising awareness about the crisis in lack of drugs for neglected diseases, and by using and strengthening existing R&D capacity in disease-endemic countries.

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team* (6/2004)	18	13	50	37
Background of Board	10	60	30	10
Amount of capital committed**	$30m	—	—	100
Amount of in-kind contribution (est)	Yes	—	—	—
R&D model/processes (est)	xxx	xxx	xxx	xxx

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Research	Y	Y	N	Y
Pre-clinical	Y	Y	N	Y
Phase I testing	Y	Y	N	Y
Phase II testing	Y	Y	N	Y
Phase III testing	Y	Y	N	Y
Regulatory approval	Y	Y	Y	Y
Manufacturing	N	N	Y	N
Distribution/'access'	N	N	Y	N
Advocacy/education	Y	Y	Y	N

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts)	9	Forecast end 2005 portfolio (# of pdts):	xxx
• Discovery	4		
• Pre-clinical:	1	• Pre-clinical:	xxx
• Phase I:	—	• Phase I:	xxx
• Phase II:	—	• Phase II:	xxx
• Phase III:	4	• Phase III:	xxx
• In-market:	—	• In-market:	xxx
Number of clinical trials:	1	Number of clinical trials:	xxx
Location of clinical trials: Burkina Faso		Location of clinical trials:	xxx

SIZE/MANAGEMENT

Number of professional employees:	8
Capital raised to date:	$30m
Number of donors:	1**
Board of Directors size:	10
Scientific Advisory Committee size (if used):	15
Policy Advisory Committee size (if used):	xxx

PUBLISHED MATERIALS

Use of:	
• Scientific blueprint	—
• Business plan	Y
• Pharmaco-economic report	—
• Access plan	—
• Advocacy plan	xxx

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value
Indian Council of Medical Research		xxx
Institut Pasteur		
Kenya Medical Research Institute		
Ministry of Health, Malaysia		
Médecins Sans Frontières		
Oswaldo Cruz Foundation		
WHO/TDR		

* Plus 10 consultants

** MSF committed to maximum support of $30m over 5 years. Does not include $2.6m budgeted for FACT malaria project

EMVI

The European Malaria Vaccine Initiative (EMVI)
Launch date: 1998
Focus: Vaccines
Target: Malaria
Website: www.emvi.org

Director: Dr. Soren Jepsen
Address: Statens Serum Institut
Artillerivej 5, 2300 Copenhagen S
Danmark

MISSION

Contribute to global efforts to control malaria by:

- providing a mechanism for accelerated development and clinical trials of malaria vaccines in Europe and developing countries
- promoting affordability and accessibility of malaria vaccines in developing countries

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	3	100	—	—
Background of Board	10	90	10	—
Amount of capital contributed	$18m*	100	—	—
Amount of in-kind contribution (est)	0	—	—	—
Ownership over Pdts produced (est)	—	100	—	—
R&D model/processes (est)	xxx	xxx	xxx	xxx

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Research	N	N	N	Y
Pre-clinical	Y	Y	N	Y
Phase I testing	Y	Y	N	Y
Phase II testing	Y	Y	N	Y
Phase III testing	N	N	N	Y
Regulatory approval	xxx	xxx	xxx	xxx
Manufacturing	N	N	N	Y
Distribution/'access'	N	N	N	Y
Advocacy	Y	Y	Y	N

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts)	10	Forecast end 2005 portfolio (# of pdts):	11
• Pre-clinical:	4	• Pre-clinical:	5
• Phase I:	4–5	• Phase I:	4
• Phase II:	0	• Phase II:	1
• Phase III:	0	• Phase III:	0
• In-market:	0	• In-market:	0
Number of clinical trials:	3	Number of clinical trials:	4
Location of clinical trials: Switzerland, UK, India, The Netherlands, Burkina Faso		Location of clinical trials:	xxx

SIZE/MANAGEMENT

Number of professional employees:	3
Capital raised to date:	$18m*
Number of donors:	6**
Board of Directors size:	10
Scientific Advisory Committee size (if used):	7
Policy Advisory Committee size (if used):	xxx

PUBLISHED MATERIALS

Use of:	
• Scientific blueprint	Y
• Business plan	Y
• Pharmaco-economic report	N
• Access plan	N
• Advocacy plan	?

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value
	xxx	xxx

* = 15 million Euros

** Donors include DANIDA/DK, DGIS/NL, Sida/SAREC/SE, DCI/IR, EC/BE, CIH/NO

FIND DIAGNOSTICS

Foundation for Innovative New Diagnostics (FIND)
Launch date: 2003
Focus: Develop diagnostics
Target: TB Initially
Website: www.finddiagnostics.org

Director: Dr. Giorgio Roscigno
Address: 71, av Louis-Casai
Case postale 93
1216 Cointrin/Geneva
Switzerland

MISSION

FIND will accelerate the development, evaluation and appropriate use of high-quality yet affordable diagnostic tools for infectious diseases in developing countries.

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	6	50	50	—
Background of Board	4	25	50	25
Amount of capital contributed	$30m	—	—	100
Amount of in-kind contribution (est)	—	—	—	—
R&D model/processes (est)	—	30	70	—

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Basic research	N	N	—	Y
Pre-clinical	Y	N	—	Y
Phase I testing	Y	N	—	Y
Phase II testing	Y	N	—	Y
Phase III testing	Y	N	—	Y
Regulatory approval	Y	Y	—	Y
Manufacturing	N	Y	—	Y
Distribution/'access'	N	Y	—	Y
Advocacy/education	N	Y	—	Y

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts)	5
• Pre-clinical:	1
• Phase I:	1
• Phase II:	1
• Phase III:	2
• In-market:	—
Number of clinical trials:	3
Location of clinical trials: Africa, Latin America, Asia	

Forecast end 2005 portfolio (# of pdts):	12
• Pre-clinical:	5
• Phase I:	1
• Phase II:	2
• Phase III:	3
• In-market:	1
Number of clinical trials:	6
Location of clinical trials: Africa, Asia, USA, E.Europe	

SIZE/MANAGEMENT

Number of professional employees:	7
Capital raised to date:	$30m
Number of donors:	1 (Gates)
Board of Directors size:	5
Scientific Advisory Committee size (if used):	8
Policy Advisory Committee size (if used):	4

PUBLISHED MATERIALS

Use of:	
• Scientific blueprint	Y
• Business plan	Y
• Pharmaco-economic report	Y
• Access plan	in process
• Advocacy plan	—

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value
Stop TB Partnership		
Biotechnology Companies (North, South)	Discussions ongoing	
Major Diagnostic Companies	Discussions ongoing	
Public Research Institutes (North, South)	Discussions ongoing	
Merck Germany	Lump sum purchase patents	n/a
Government Institutions	Discussions ongoing	

GMP
GLOBAL MICROBICIDE PROJECT

Global Microbicide Project (GMP)
Launch date: 2000
Focus: Microbicides
Target: STI, HIV/AIDS
Website: www.gmp.org

Director: Dr. Michael J.K. Harper
Address: CONRAD
1611 N. Kent St., Suite 806
Arlington, VA 22209-2111
USA

MISSION

To develop vaginal methods that will protect women against sexually transmitted infections, including HIV/AIDS.

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	6	100	0	0
Background of Board	10	83	17	0
Amount of capital contributed	$64m*	45	5	50
Amount of in-kind contribution (est)	$3m	4	96	—
R&D model/processes (est)	Yes	—	—	—

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Research	Y	Y	Y	Y
Pre-clinical	Y	Y	Y	Y
Phase I testing	Y	Y	Y	Y
Phase II testing	Y	Y	N	Y
Phase III testing	Y	Y	N	Y
Regulatory approval	Y	Y	Y	Y
Manufacturing	Y	Y	N	Y
Distribution/'access'	N	N	N	Y
Advocacy	Y	Y	N	Y

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts)	16
• Pre-clinical:	8
• Phase I:	7
• Phase II:	0
• Phase III:	1
• In-market:	0
Number of clinical trials:	9
Location of clinical trials: 5 countries	

Forecast end 2005 portfolio (# of pdts):	12
• Pre-clinical:	4
• Phase I:	7
• Phase II:	0
• Phase III:	2
• In-market:	0
Number of clinical trials:	9
Location of clinical trials: 9 countries	

SIZE/MANAGEMENT

Number of professional employees:	14
Capital raised to date:	$64m*
Number of donors:	9*
Board of Directors size: Strategic Advisory Board	10
Scientific Advisory Committee size (if used):	12
Policy Advisory Committee size (if used):	n/a

PUBLISHED MATERIALS

Use of:	
• Scientific blueprint	Y
• Business plan	Y
• Pharmaco-economic report	N
• Access plan	Y
• Advocacy plan	N

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value
Partners: ITM, WHO, FHI, Biosyn, Indevus, MedTech, OSEL, PATH, Personal Care Products, Polydex Pharm., ReProtect	Cash and in kind	$3m

* Includes funds awarded to CONRAD (GMP parent) by USAID, CDC, and NIH for microbicide research

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT
It's time for a faster cure

Global Alliance for TB Drug Development
Launch date: 2000
Focus: Develop drugs
Target: TB
Website: www.tballiance.org

Director: Dr. Maria Freire
Address: 80 Broad Street, 31st Floor
New York, NY 10004
USA

MISSION

To accelerate the discovery and/or development of affordable new TB drugs that will:

- Shorten the duration of TB treatment or otherwise simplify its completion
- Improve the treatment of latent TB infection
- Be effective against multi-drug resistant TB (MDR-TB)

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	8	50	50	—
Background of Board	11	50	40	10
Amount of capital contributed	$42.2m	4.7	0.3	94.9
Amount of in-kind contribution (est)	$1.6m	80	6	14
R&D model/processes (est)	—	10	85	5

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Basic research	N	N	N	N
Pre-clinical	Y	Y	N	Y
Phase I testing	N	Y	N	Y
Phase II testing	Y	Y	N	Y
Phase III testing	N	N	N	Y
Regulatory approval	Y	Y	Y	Y
Manufacturing	N	N	N	Y/N
Distribution/'access'	N	Y	N	Y/N
Advocacy	Y	Y	Y	Y

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts) 10
- Pre-clinical: 9
- Phase I: 0
- Phase II: 1
- Phase III: 0
- In-market: 0

Number of clinical trials: n/a
Location of clinical trials: Africa, Asia, South America

Forecast end 2005 portfolio (# of pdts):
- Pre-clinical: 12
- Phase I: 2
- Phase II: 1
- Phase III: 0
- In-market: 0

Number of clinical trials:
Location of clinical trials: Africa, Asia, South America

SIZE/MANAGEMENT

Number of professional employees: 14
Capital raised to date: $42.2m
Number of donors: 5
Board of Directors size: 10
Scientific Advisory Committee size (if used): 14
Policy Advisory Committee size (if used): 30

PUBLISHED MATERIALS

Use of:
- Scientific blueprint: Y
- Business plan: Y
- Pharmaco-economic report: Y
- Access plan: xx
- Advocacy plan: xx

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value
Gates & Rockefeller Foundations	Funding	$25m/$15m = $40m (grants)
Dutch Ministry of Development Cooperation/WHO	Funding	$2m in (grant)
NIAID	Pre-clinical capacity and in-kind funding	$1.5m (in kind)
GSK	Seconded expertise	$0.1m (in-kind)
CDC & TBTC, IUATLD, MRC South Africa	Clinical Trials & Scientific Networking	n/a
Research Triangle Institute	Expertise	n/a
Bristol Myers Squibb Foundation/other donors	Funding	$0.2m (grant and donations)

Human Hookworm Vaccine Initiative (HHVI)
Launch date: 2000
Focus: Vaccines
Target: Hookworm
Website: www.sabin.org

Director: Peter Hotez MD PhD
Address: Hosted by Albert Sabin Vaccine Institute
161 Cherry Street
New Canaan, CT 06840-4818

MISSION

The **Human Hookworm Vaccine Initiative** (HHVI) is developing a multi-antigen Human Hookworm Vaccine comprised of both third-stage infective larval (L3) and adult-stage antigens of human hookworms. The first antigen component of this vaccine is the *Na*-ASP-2 Hookworm Vaccine, comprised of a single recombinant protein from *Necator americanus* L3. The intended use of the *Na*-ASP-2 Hookworm Vaccine is induction of a measurable antibody response and, when given to individuals at risk for hookworm infection confer protection or partial protection of these individuals from infection or re-infection with hookworm. This would reduce worm burden and its concomitant outcomes, hookworm anemia and disease.

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	4	10	50	40
Background of Board*	12	25	75	—
Amount of capital contributed	$20m	5	—	95
Amount of in-kind contribution (est)	4	10	60	30
R&D model/processes (est)	1	5	5	90

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Research	Y	Y	Y	N
Pre-clinical	Y	Y	Y	Y
Phase I testing	N	Y	Y	N
Phase II testing	N	Y	Y	Y
Phase III testing	N	Y	Y	Y
Regulatory approval	Y	Y	Y	Y
Manufacturing	Y	Y	Y	Y
Distribution/'access'	N	Y	—	—
Advocacy/education	Y	Y	Y	Y

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts)	6	Forecast end 2005 portfolio (# of pdts):	6
• Pre-clinical:	6	• Pre-clinical:	5
• Phase I:	—	• Phase I:	2
• Phase II:	—	• Phase II:	—
• Phase III:	—	• Phase III:	—
• In-market:	—	• In-market:	—
Number of clinical trials:	—	Number of clinical trials:	2
Location of clinical trials:		Location of clinical trials: USA, Brazil	

SIZE/MANAGEMENT

Number of professional employees:	30
Capital raised to date:	$20m
Number of donors:	4
Board of Directors size:*	12
Scientific Advisory Committee size:	7
Policy Advisory Committee size (if used):	—

PUBLISHED MATERIALS

Use of:	
• Scientific blueprint	1
• Business plan	—
• Pharmaco-economic report	—
• Access plan	—
• Advocacy plan	—

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value
George Washington University, Washington, DC FIOCRUZ, Brazil London School of Hygiene and Tropical Medicine, UK Queensland Institute for Medical Research, Australia	Research, Product Development and Clinical Testing	

* Sabin Board/SAC

International AIDS Vaccine Initiative
Launch date: 1996
Focus: Vaccines
Target: HIV/AIDS
Website: www.iavi.org

Director: Dr. Seth Berkley
Address: 110 William Street, floor 27
NY, NY 10038-3901 USA
Regional offices in Amsterdam, Nairobi and New Delhi

MISSION

To ensure the development of safe effective accessible preventive HIV vaccines for use throughout the world

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	11	27	73	—
Background of Board	17	53	47	—
Amount of capital contributed	$350m	45	10	45
Amount of in-kind contribution (est)	$20m	xxx	100	xxx
R&D model/processes (est)	xxx	xxx	xxx	xxx

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Research	Y	Y	Y	Y
Pre-clinical	Y	Y	Y	Y
Phase I testing	Y	Y	Y	Y
Phase II testing	Y	Y	Y	Y
Phase III testing	N	Y	N	Y
Regulatory approval	Y	Y	Y	X
Manufacturing	Y	Y	N	Y
Distribution/'access'	Y	N	Y	Y
Advocacy/education	Y	Y	—	Y

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts)
- Pre-clinical: 20
- Phase I: 5
- Phase II: 1
- Phase III: 0
- In-market: 0

Number of clinical trials: 15
Location of clinical trials: Belgium, Germany, Kenya, South Africa, Switzerland, Uganda, UK, UAS

Forecast end 2005 portfolio (# of pdts):
- Pre-clinical: 20
- Phase I: 10
- Phase II: 2
- Phase III: 1
- In-market: 0

Number of clinical trials: 20
Location of clinical trials: North America, Europe, India, Africa, China

SIZE/MANAGEMENT

Number of professional employees:	125
Capital raised to date:	$350m
Number of donors:	50
Board of Directors size:	17
Scientific Advisory Committee size:	12
Policy Advisory Committee size:	16

PUBLISHED MATERIALS

Use of:
- Scientific blueprint: Y
- Business plan: Y
- Pharmaco-economic report: Y
- Access plan: Y
- Advocacy plan: Y

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value
More than 50 partners operating in 23 countries (see web site)	All types	Too numerous to count

Institute for OneWorld Health
Launch date: 2000
Focus: Drugs and vaccines
Target: Initially Leishmaniasis (India) and Chagas (LA)
Website: www.oneworldhealth.org

CEO & Founder: Dr. Victoria Hale
Address: 580 California St
Suite 900
San Francisco, CA 94104

MISSION

Develop safe, effective, and affordable, new medicines for people afflicted with infectious diseases in the developing world. Target infectious diseases in the developing world that lack adequate therapies such as leishmaniasis, Chagas disease, diarrheal diseases, schistosomiasis and malaria.

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	4	25	75	—
Background of Board	6	17	67	17
Amount of capital contributed	$11.3m	—	—	100
Amount of in-kind contribution (est)	$4.5m	33	67	—
R&D model/processes (est)	—	—	—	—

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Research	N	N	N	N
Pre-clinical	Y	Y	N	Y
Phase I testing	Y	Y	Y	N
Phase II testing	Y	Y	Y	N
Phase III testing	Y	Y	Y	N
Regulatory approval	Y	Y	Y	N
Manufacturing	Y	Y	N	Y
Distribution/'access'	N	Y	Y	N
Advocacy/education	Y	Y	Y	N

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts)	5	Forecast end 2005 portfolio (# of pdts):	8
• Pre-clinical:	3	• Pre-clinical:	6
• Phase I:	0	• Phase I:	1
• Phase II:	1	• Phase II:	0
• Phase III:	1	• Phase III:	1
• In-market:	—	• In-market:	1
Number of clinical trials:	2	Number of clinical trials: (+ Ph IV)	5
Location of clinical trials: India		Location of clinical trials: Asia	

SIZE/MANAGEMENT

Number of professional employees:	25
Capital raised to date:	$11.3m
Number of donors:	3
Board of Directors size:	6
Scientific Advisory Committee size (if used):	16
Policy Advisory Committee size (if used):	—

PUBLISHED MATERIALS

Use of:	
• Scientific blueprint	Y
• Business plan	N
• Pharmaco-economic report	N
• Access plan	N
• Advocacy plan	N

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value
Celera Genomics	Develop CRA-3316 for Chagas	Not disclosed
NIH	Preclinical testing	$1.5m
TDR/WHO	Paromomycin collaboration	Not disclosed
Walter Reed Army Institute of Research	Consulting	Not disclosed
UC Santa Barbara	Patent donation for schistosomiasis	Not disclosed
Yale/University of Washington	Develop azoles for Chagas	Not disclosed

International Partnership for Microbicides (IPM)
Launch date: 2002
Focus: Pdt to reduce trans of HIV/other pathogens
Target: HIV/AIDS
Website: www.ipm-microbicides.org

Director: Dr. Zeda F. Rosenberg
Address: 1010 Wayne Avenue, Suite 1450
Silver Spring, MD 20910
USA

MISSION

To accelerate the discovery, development and accessibility of safe and effective microbicides to prevent transmission of HIV for women in developing countries. IPM was established to identify and address gaps or bottlenecks that may limit the development, clinical testing, approval, distribution, and use of microbicides.

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	6	50	50	—
Background of Board	10	70	30	—
Amount of capital contributed	$94.5m	21	—	79
Amount of in-kind contribution (est)	250k	—	100	—
R&D model/processes (est)	—	10	90	—

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Research	Y	Y	Y	Y
Pre-clinical	Y	Y	Y	Y
Phase I testing	Y	Y	Y	Y
Phase II testing	N	Y	Y	Y
Phase III testing	N	Y	Y	Y
Regulatory approval	Y	Y	Y	Y
Manufacturing	N	Y	Y	Y
Distribution/'access'	N	N	N	Y
Advocacy/education	Y	Y	Y	Y

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts)	3	Forecast end 2005 portfolio (# of pdts):	6
• Pre-clinical:	3	• Pre-clinical:	5
• Phase I:	1–2	• Phase I:	3
• Phase II:	0	• Phase II:	1
• Phase III:	0	• Phase III:	0
• In-market:	0	• In-market:	0
Number of clinical trials:	1	Number of clinical trials:	4
Location of clinical trials: Belgium, UK		Location of clinical trials: International	

SIZE/MANAGEMENT

Number of professional employees:	8
Capital raised to date:	$94m
Number of donors:	9
Board of Directors size:	10
Scientific Advisory Committee size (if used):	10
Policy Advisory Committee size (if used):	10

PUBLISHED MATERIALS

Use of:	
• Scientific blueprint	Y
• IPM business plan	Y
• Pharmaco-economic report (Rockefeller Reports)	Y
• Access plan (Rockefeller Reports)	Y
• Advocacy plan (Rockefeller Reports)	Y

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value
Tibotec/Johnson & Johnson	Phase I trial support	$250,000

Microbicides Development Programme (MDP)
Launch date: 2001
Focus: Pdt to reduce transmission of HIV/AIDS
Target:
Website: www.mdp.mrc.ac.uk

Director: **Profs. Jonathan Weber/Janet Darbyshire,**
Address: **c/o Imperial College Winston Churchill Wing, Faculty of Medicine, St Mary's Campus, Norfolk Place, London W2 1PG**

MISSION

The **MDP** aims to evaluate potential microbicides in vitro, to carry out safety studies in the UK and Africa, to conduct social science research into acceptability and barriers to uptake of products, complete phase III effectiveness trials and to facilitate marketing and access to a successful microbicide.

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	8	100	—	—
Background of Board	21	100	—	—
Amount of capital contributed	$27m	100	—	—
Amount of in-kind contribution (est)	Yes	—	—	—
R&D model/processes (est)	Yes	—	—	—

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Research	Y	Y	Y	N
Pre-clinical	Y	Y	Y	N
Phase I testing	Y	Y	Y	N
Phase II testing	Y	Y	Y	N
Phase III testing	N	Y	Y	N
Regulatory approval	N	N	—	—
Manufacturing	N	N	N	Y
Distribution/'access'	N	N	N	Y
Advocacy/education	N	N	N	Y

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts)	3
• Pre-clinical:	—
• Phase I:	1
• Phase II:	1
• Phase III:	—
• In-market:	—
Number of clinical trials:	2
Location of clinical trials: UK, Uganda	

Forecast end 2005 portfolio (# of pdts):	2
• Pre-clinical:	—
• Phase I:	—
• Phase II:	—
• Phase III:	2
• In-market:	—
Number of clinical trials:	1
Location of clinical trials: S. Africa, Zambia, Uganda, Tanzania, Cameroon, Swaziland	

SIZE/MANAGEMENT

Number of professional employees:	200
Capital raised to date:	$27m
Number of donors:	1
Board of Directors size:	21
Scientific Advisory Committee size (if used):	8
Policy Advisory Committee size (if used):	No

PUBLISHED MATERIALS

Use of:	
• Scientific blueprint	N
• Business plan	N
• Pharmaco-economic report	N
• Access plan	N
• Advocacy plan	N

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value
UK Dept. for Intl. Development		$27m
Indevus		Gel (?)
ML Laboratories		Gel (?)
Dow Pharmaceuticals/NY Blood Center		Gel (?)

Medicines for Malaria Venture
A nonprofit foundation

Medicines for Malaria Venture (MMV)
Launch date: 1999
Focus: Drugs
Target: Malaria
Website: www.mmv.org

Director: Dr. Chris Hentschel
Address: PO Box 1826
20, rte de Pré-Bois,
1215 Geneva 15
Switzerland

MISSION

To bring public, private and philanthropic sector partners together to fund and manage the discovery, development and registration of new medicines for the treatment and prevention of malaria in disease-endemic countries.
Goal: one new drug every five years with a first one by 2010.

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	11	—	100	—
Background of Board	9	22	66	11
Amount of capital contributed	$107m	30.1	1	68.9
Amount of in-kind contribution (est)	$25m	2	98	—
R&D model/processes (est)	—	—	100	—

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house*	Out-sourced
Research	Y	Y	N	Y
Pre-clinical	Y	Y	N	Y
Phase I testing	Y	Y	N	Y
Phase II testing	Y	Y	N	Y
Phase III testing	Y	Y	N	Y
Regulatory approval	Y	Y	N	Y
Manufacturing	Y	Y	N	Y
Distribution/'access'	Y	Y	N	Y
Advocacy/education	Y	Y	Y	Y

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts)	21	Forecast end 2005 portfolio (# of pdts):	xxx
• Pre-clinical:	6	• Pre-clinical:	3
• Phase I:	3	• Phase I:	5
• Phase II:	1	• Phase II:	7
• Phase III:	2	• Phase III:	5
• In-market:	xxx	• In-market:	1
Number of clinical trials:	7	Number of clinical trials:	17
Location of clinical trials: Africa, Asia, Europe		Location of clinical trials: Africa, Asia, Latin America	

SIZE/MANAGEMENT

Number of professional employees:	11
Capital raised to date:	$107m
2003 Annual Budget:	$19.2m
Number of donors:	11
Board of Directors size:	9
Scientific Advisory Committee size (if used):	11
Policy Advisory Committee size (if used):	No

PUBLISHED MATERIALS

Use of:	
• Scientific blueprint	N
• Business plan/update	Y
• Pharmaco-economic report	N
• Access plan	N
• Advocacy plan	N

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value
Roche, Novartis, Ranbaxy, Shin Poong Pharma Co, Bayer, Immtech, Jacobus Pharma USA, Paratek Pharma, GSK-Tres Cantos, GSK-UK, GSK-USA, Holleykin Pharma/China	Various in-kind	$25m

* MMV staff closely supervise/monitor work of contractors/collaborators.

Malaria Vaccine Initiative (MVI)
Launch date: 1999
Focus: Vaccines
Target: Malaria
Website: www.malariavaccine.org

Director: Melinda Moree
Address: 1455 NW Leary Way
Seattle, WA 98107
USA

MISSION

MVI's mission is to accelerate the development of promising malaria vaccines and ensure their availability and accessibility in the developing world.

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	5	20	40	40
Background of Board	n/a	n/a	n/a	n/a
Amount of capital contributed	$150m	0	<1	>99
Amount of in-kind contribution (est)	Not quantified	—	—	—
R&D model/processes (est)	—	20	80	—

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Research	N	N	—	—
Pre-clinical	Y	Y	N	Y
Phase I testing	Y	Y	N	Y
Phase II testing (pilot efficacy)	Y	Y	N	Y
Phase III testing (registration trial)	N	Y	N	Y
Regulatory approval	Y	Y	Y	Y
Manufacturing	—	—	—	Y
Distribution/'access'	Y	Y	Y	Y
Advocacy/education	Y	Y	Y	Y

PORTFOLIO STRATEGY

January 2004 portfolio (# of vaccine concepts)	15
• Pre-clinical:	9
• Phase I:	3
• Phase II: (pilot efficacy)	3
• Phase III: (registration trial)	0
• In-market:	0
Number of clinical trials:	7
Location of clinical trials: Europe, USA, Africa	

January 2005 portfolio (# of vaccine concepts):	18
• Pre-clinical:	10
• Phase I:	4
• Phase II: (pilot efficacy)	4
• Phase III: (registration trial)	0
• In-market:	0
Number of clinical trials:	10
Location of clinical trials: Europe, USA, Africa	

SIZE/MANAGEMENT

Number of professional employees:	16
Capital raised to date:	$150m
Number of donors:	2
Board of Directors size:	—
Scientific Advisory Committee size (if used):	varies
Policy Advisory Committee size (if used):	—

PUBLISHED MATERIALS

Use of:	
• Scientific blueprint	Y
• Business plan	Y
• Pharmaco-economic report	due 2005
• Access plan	—
• Advocacy plan	Y

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value

All of MVI's partners and collaborators (academic, government, industry, non-profit) contribute resources to the projects. These in-kind contributions have not been quantified.

Pediatric Dengue Vaccine Initiative (PDVI)
Launch date: 2002
Focus: Vaccines
Target: Pediatric dengue
Website: www.pdvi.org

Director: Dr. Scott Halstead
Address: International Vaccine Institute
Kwanak-gu Seoul POB 14
Republic of Korea

MISSION

PDVI will raise awareness and work with public and private partners in the North and the South to accelerate the development and introduction of a dengue vaccine that is safe, accessible and affordable to poor children in endemic countries. PDVI is designed to augment and supplement efforts of the private sector in dengue vaccine testing for efficacy and safety.

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	4	75	0	25
Background of Board	9	89	11	—
Amount of capital contributed	$56m	0.5	0.5	99
Amount of in-kind contribution (est)	—	—	—	—
R&D model/processes (est)	$250	65	35	0

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Research	Y	Y	—	Y
Pre-clinical	Y	Y	—	Y
Phase I testing	N	Y	—	Y
Phase II testing	N	Y	—	Y
Phase III testing	N	Y	—	Y
Regulatory approval	—	—	—	—
Manufacturing	N	N	—	—
Distribution/'access'	N	N	—	—
Advocacy/education	Y	Y	Y	—

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts)	0*	Forecast end 2005 portfolio (# of pdts):	0*
• Pre-clinical:	—	• Pre-clinical:	—
• Phase I:	—	• Phase I:	—
• Phase II:	—	• Phase II:	—
• Phase III:	—	• Phase III:	—
• In-market:	—	• In-market:	—
Number of clinical trials:	—	Number of clinical trials:	1
Location of clinical trials:	—	Location of clinical trials:	xxx

SIZE/MANAGEMENT

Number of professional employees:	4
Capital raised to date:	$56m
Number of donors:	10*
Board of Directors size:	9
Scientific Advisory Committee size:	13
Policy Advisory Committee size:	—

PUBLISHED MATERIALS

Use of:	
• Scientific blueprint	N
• Business plan	Y
• Pharmaco-economic report	Y
• Access plan	N
• Advocacy plan	N

* Mature field with several private sector companies developing dengue vaccines de novo or those invented in the public sector. PDVI's strategy is to get ahead of development funding and prepare Phase III trial sites to be made available at reduced cost to manufacturers specifically for pediatric testing.

** Funders include Gates ($55m), Rockefeller, Aventis Pasteur, GSK, Acambis, Novartis, Ellison, the US Navy, the US Army, Jackson Foundation

pneumoADIP

PneumoADIP
Launch date: 2003
Focus: Vaccines
Target: Pneumonia and meningitis
Website: www.preventpneumo.org

Executive Director: Dr. Orin Levine
Address: Johns Hopkins University
Bloomberg School of Public Health
Baltimore, MD 21205-2179
USA

MISSION

Our mission is to improve child survival and health by accelerating the evaluation of and access to, new life saving pneumococcal vaccines for the world's children.

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	7	71	29	—
Background of Board*	xxx	xxx	xxx	xxx
Amount of capital contributed	$30m	—	—	100
Amount of in-kind contribution (est)**	100,000	50	50	—
R&D model/processes (est)	xxx	xxx	xxx	xxx

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Research	Y	Y	Y	Y
Pre-clinical/surveillance activities	Y	Y	N	Y
Phase I testing	N	N	N	Y
Phase II testing	N	Y	—	—
Phase III testing	N	Y	—	—
Regulatory approval	Y	Y	N	Y
Manufacturing	N	N	—	—
Sales/distribution	N	N	—	—
Advocacy/education	Y	Y	Y	Y

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts) ***	—	Forecast end 2005 portfolio (# of pdts):	—
• Pre-clinical:	—	• Pre-clinical:	—
• Phase I:	—	• Phase I:	—
• Phase II:	—	• Phase II:	—
• Phase III:	—	• Phase III:	2
• In-market:	—	• In-market:	—
Number of clinical trials:***	—	Number of clinical trials:	(2006)
Location of clinical trials:	—	Location of clinical trials:	—

SIZE/MANAGEMENT

Number of professional employees:	7
Capital raised to date:	$30m
Number of donors:	1 (GAVI)
Board of Directors size:*	7
Scientific Advisory Committee size:****	xxx
Policy Advisory Committee size (if used):	6

PUBLISHED MATERIALS

Use of:*****	
• Scientific blueprint	Y
• Business plan	—
• Pharmaco-economic report	Y
• Access plan	—
• Advocacy Plan	Y

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value
WHO	xxx	xxx

* Management committee sub-group of GAVI Board. Meets twice a year.
** Logo development and other communications support
*** Active phase III trials in Gambia and Philippines and S.Africa by 2 private sector companies
**** No standing committee; expert panel is convened as needed
***** Developing communications plan and economic report

ROTAVIRUS VACCINE PROGRAM

Rotavirus Vaccine Accel Devel & Intro Plan (Rota-ADIP)
Launch date: 2003
Focus: Vaccines
Target: Rotavirus
Website: www.rotavirusvaccine.org

Director: John Wecker, Ph.D.
Address: Rotavirus Vaccine Program, 1455 NW Leary Way, Seattle, WA 98107 USA

MISSION

To reduce child morbidity and mortality from diarrheal disease by accelerating the availability of rotavirus vaccines appropriate for use in developing countries.

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	6	83	17	—
Background of Board*	6	83	17	—
Amount of capital contributed	$30m	—	—	100
Amount of in-kind contribution (est)	xxx	—	—	—
R&D model/processes (est)	—	50	100	—

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Research	N	N	—	—
Pre-clinical	N	N	—	—
Phase I testing	N	N	—	—
Phase II testing	N	Y	N	Y
Phase III testing	N	Y	N	Y
Regulatory approval	xx	xx	xx	xx
Manufacturing	N	N	—	—
Distribution/'access'	N	Y	Y	—
Advocacy/education	Y	Y	Y	N

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts)	2	Forecast end 2005 portfolio (# of pdts):	2
• Pre-clinical:	—	• Pre-clinical:	—
• Phase I:	—	• Phase I:	—
• Phase II:	2	• Phase II:	—
• Phase III:	—	• Phase III:	2
• In-market:	—	• In-market:	—
Number of clinical trials:	—	Number of clinical trials:	4
Location of clinical trials:		Location of clinical trials: Africa, Asia	

SIZE/MANAGEMENT

Number of professional employees:	6
Capital raised to date:	$30m
Number of donors:	1
Board of Directors size:	6
Scientific Advisory Committee size:	4
Policy Advisory Committee size (if used):	—

PUBLISHED MATERIALS

Use of:	
• Scientific blueprint	N
• Business plan	N
• Pharmaco-economic report	N
• Access plan	N
• Advocacy plan	N

LIST OF PARTNERS

	Contribution type	In-kind contribution financial value
World Health Organization	Human Resources	xxx
CDC	Human Resources	

* GAVI Management committee

SAAVI
SOUTH AFRICAN AIDS VACCINE INITIATIVE

South African AIDS Vaccine Initiative
Launch date: 1999
Focus: Vaccine coord (S.Africa)
Target: HIV/AIDs
Website: www.saavi.org.za

Director: Dr. Tim Tucker
Address: Francie Van Zijl Drive
Medical Research Council
Parow Valley, 7505

MISSION

A national body coordinating the research, development and testing of HIV/AIDS vaccines in South Africa with the aim of producing an affordable, effective and locally relevant preventative HIV/AIDS vaccine.

RELATIVE CONTRIBUTION

	Total size	Percent public (%)	Percent private (%)	Donor/foundation/ other (%)
Background of Management Team	10	40	60	—
Background of Board	10	50	50	40
Amount of capital contributed	$45m	77	23	—
Amount of in-kind contribution (est)	$2m/year	90	10	—
Ownership over pdts produced (est)	All	—	—	—
R&D model/processes (est)	—	—	—	—

SCOPE OF ACTIVITIES

	Today	Future (2005+)	Activity managed	
	Yes/No	Yes/No	In-house	Out-sourced
Research	Y	Y	Y	Y/N
Pre-clinical	Y	Y	Y	Y/N
Phase I testing	N	Y	Y	Y
Phase II testing	N	N	Y	Y
Phase III testing	N	N	Y	Y
Regulatory approval	Y	Y	Y/N	Y/N
Manufacturing	Y	Y	N	Y/N
Sales/distribution	N	N	Y/N	N
Advocacy	Y	Y	Y	N

PORTFOLIO STRATEGY

Current 2004 portfolio (# of pdts)	8	Forecast end 2005 portfolio (# of pdts):	8
• Pre-clinical:	6	• Pre-clinical:	5
• Phase I:	1+(2)	• Phase I:	2+(?)
• Phase II:	—	• Phase II:	(1)
• Phase III:	—	• Phase III:	—
• In-market:	—	• In-market:	—
Number of clinical trials:	—	Number of clinical trials:	2
Location of clinical trials: S. Africa, USA		Location of clinical trials: S. Africa, USA	

SIZE/MANAGEMENT

Number of professional employees:	200
Capital raised to date:	$45m
Number of donors:	±7
Board of Directors size:	10
Scientific Advisory Committee size (if used):	13
Policy Advisory Committee size (if used):	5

PUBLISHED MATERIALS

Use of:	
• Scientific blueprint	Y
• Business plan	(Y)
• Pharmaco-economic report	Y
• Access plan	Y
• Advocacy road map	(Y)

LIST OF PARTNERS/STAKEHOLDERS

	Contribution type*	In-kind contribution financial value
Eskom	SAR 67.5m	
Dept. of Health, Dept. of Science and Tech.	SAR105m	
SA MRC	—	—
NIH	SAR52.2m	Yes, ?
EU	SAR9.9m	
UCT, U.S., U, Natal	}	SAR}
Chiron, Cobra, Therion, Biovac, etc. etc.	}	SAR}70m

* Over 5 years

ANNEX 9C

PPPs and product development: Innovative financing opportunities and the need for a 'business case' approach

Amie Batson (World Bank), Rajiv Shah (Bill & Melinda Gates Foundation), Chris Gingerich (Consultant, Bill & Melinda Gates Foundation) and J. Niels Rosenquist (Consultant, World Bank)

Executive summary

Given the sheer size of the looming financing challenge, PPPs need to look beyond traditional public and donor financing sources if they are to meet the significant challenges of bringing multiple orphan products to market. This paper looks beyond traditional sources of financing for PPPs and analyses several 'from where' and 'how to' opportunities for bringing new money to the table.

The paper is divided into three main sections:

- Financing opportunity – Investors and the capital markets
- Financing opportunity – Development assistance for health
- The business case – A tool for attracting financing

Much of the information presented in this paper is the result of research currently being undertaken in several working groups of which the authors are key participants. Additional components of the discussion are based on learnings from early-stage efforts to implement some of the concepts discussed in the paper. The final section of the paper – which focuses on the business case method for presenting a financing project proposal to funders – is based in part on work currently being undertaken by a major funding resource that will reinvent the way that they approach grantmaking. Our belief is that to the extent that PPPs are able to develop a competency in presenting their funding proposals within a business case framework, they will be better positioned to obtain financing from all potential donors, whether traditional donors or new funding sources.

Key conclusions from each of the major sections are presented below.

Financing opportunity – Investors and the capital markets

The primary benefit of the tax-exempt debt and securitization concepts are that they both shift money forward in time. However, in both cases the organization is leveraging existing financial resources to obtain immediate financing – neither solution brings 'new money' to the table.

In contrast, both project finance and put options do attract 'new money'. However, the project finance concept hinges entirely on the presence of an off-take agreement, and the put-options concept can be realized only if there exists an entity willing to guarantee future purchase of the product at a fixed price should the option be exercised. In both of these instances, the ability to attract new money is based entirely on the premise of guaranteed future market for the product in question.

Investors seek to minimize the risk embedded in their future investment returns. Within the context of product development (PD) financing, the best available risk minimization strategy is to guarantee a future market for the product in question. Thus, in order to attract investor financing it is necessary to have a purchase contract in place.

Health product purchasers seek to minimize risk with regard to procurement. Within the context of PD financing, purchasers will prefer to enter into off-take agreements and underwrite put options as opposed to financing risky product development activities directly.

Donors and partners are as focused on investment returns as are investors and purchasers, yet they may have the highest overall risk tolerance. Donors may be willing to finance product development directly – especially if they are willing to make the necessary long-term financial commitment.

Gordon Brown's IFF proposal – A securitization example

We also provide a brief discussion of the International Finance Facility (IFF) proposal. Key potential benefits of the IFF derive from its 'front-loaded' financing profile. Costly introduction periods for vaccines or drugs including introduction pricing, up-front infrastructure investment and potential contributions to time-limited campaigns around polio and measles all may benefit from the way in which securitization makes long-term donor funding commitments available in the near term. Front-loaded financing may also enable accelerated price maturity in vaccine markets, furthering country sustainability goals.

Financing opportunity – Development assistance for health

Traditional mechanisms often fail to value and support global public goods such as product development. Nevertheless, systematically approaching major bilateral and multilateral sources of funding is critical to obtaining necessary resources.

New financing mechanisms, whether new mechanisms at the World Bank or within the context of the US government's Millennium Challenge Account (MCA), represent a significant opportunity for funding.

Understanding country systems for priority setting and developing country champions for the development and early introduction of key products represent an important step for seeking bilateral or multilateral resources.

Multilateral grant funds and procurement mechanisms – such as the Vaccine Fund and perhaps a GFATM with more of a centralized leadership role in commodity procurement – can help create real market demand and thereby help unlock significant project financing for product development.

The business case – A tool for attracting financing

Given that investors and donors do not operate on limitless funds, both for-profit investors and not-for-profit funders must employ business-savvy strategies to evaluate potential investments. Many investors/funders in both sectors assume a portfolio perspective, distributing their investments across multiple specific objectives, and diversifying risk/benefit relationships within those objectives. The review processes they use to evaluate applicants increasingly reflect this perspective and rely heavily on the 'business case' model of presentation. Thus applicants seeking funding from for-profit or not-for-profit investors must become adept at presenting their proposals as business cases if they are to communicate the value of their project and funding proposal effectively.

As potential recipients of investment funds, PPPs must develop new competencies in this business case presentation style. Armed with these tools for making business- or financial-style requests for funding, PPPs will be better equipped to apply to diverse and multiple investors and should have increasing success in obtaining funding.

Introduction and background

The past four decades have seen few real breakthroughs in the development and introduction of health products in resource-poor settings. Despite tremendous advances in biomedical science and technology, few innovations have been developed to reduce the tremendous burden of disease of communicable disease in developing countries. However, the need to address this lack of innovation in global health has received significant new attention in the past several years. A range of public-private partnerships now exists to accelerate product development. The Vaccine Fund was created to finance the introduction of new and underused vaccines, while the United Nations created the Global Fund for AIDS, TB, and Malaria. Building on these efforts, Jim Wolfensohn, president of the World Bank, assembled in 2001 the 'Out-of-the-Box' (OOTB) group[1] to "create, improve upon, and validate new strategies and incentives to accelerate the development and use of priority health products for developing countries...".

The group concluded that a strategy of minimizing development costs and risks while guaranteeing future revenues is fundamental to accelerating the development of new health technologies targeting the world's poorest countries. The following is a list of the OOTB group's initial recommendations for further investigation:[2]

[1] The group consisted of senior leaders from industry and the public sector, with particular focus on representation by finance professionals specializing in health care.

[2] See *Out of the Box Meeting Notes*, July 2001. (http://www.gaviftf.org/forum/background_docs.html)

- **Investing in early R&D**: The public sector should become more active in reviewing and managing R&D portfolios relevant to priority diseases.
- **Investing in manufacturing plants**: The public sector can mitigate risk and influence competition via targeted investments in productive capacity.
- **Establish not-for-profit subsidiaries**: PPPs should explore opportunities to create not-for-profit divisions focused on specific vaccines.
- **Long-term purchase guarantees**: Given the fundamental barriers of risk and market uncertainty, long-term purchase guarantees are likely to be a necessary part of any solution.
- **Role of World Bank/International Development Association (IDA) in purchase guarantees**: Although the World Bank is not involved in the purchase of vaccines, it does have tremendous resources available to developing countries and should continue to explore innovative concepts to facilitate the purchasing of vaccines by developing countries.
- **'Venture capital' approach**: Money may be invested in companies developing priority vaccines in exchange for equity or 'access stakes'.[1]
- **Innovative use of capital markets**: The capital markets and related financing mechanisms may be tapped as new sources of funding for global public goods.

Many of the above recommendations are relevant to PPPs as they contemplate the coordination of vaccine PD activities, including expensive phase III clinical trials. Given the sheer size of the looming financing challenge, PPPs need to look beyond traditional public and donor financing sources if they are to meet the significant upcoming challenges of bringing multiple orphan products to market.

This paper looks beyond traditional sources financing for PPPs and analyses several 'from where' and 'how to' opportunities for bringing new money to the table. The paper is divided into three main sections:

- Financing opportunity – Investors and the capital markets
- Financing opportunity – Development assistance for health
- The business case – A tool for attracting financing

Much of the information presented in this paper is the result of research currently being undertaken in several working groups of which the authors are key participants. Additional components of the discussion are based on information from early-stage efforts to implement some of the concepts discussed in the paper. The final section of the paper, which focuses on the business case method for presenting a financing project proposal to funders, is based in part on work currently being undertaken by a major funding resource which will reinvent the way that they approach grant-making.

Our belief is that if PPPs are able to develop a competency in presenting their funding proposals within a business case framework, they will be in a better position to obtain financing from all potential donors, whether traditional donors or new funding sources.

Financing opportunity 1 – Investors and the capital markets

Given the size and prominence of capital markets institutions such as the stock and bond markets, and recognizing the fundamental role played by capital markets institutions such as commercial and investment banks, it is apparent that the they are a critical component to nearly every sector of the economy. Thus, the question remains as to why the capital markets have not been of equal prominence within the context of developing new global health products for the world's poorest countries? Put differently, what opportunities exist to leverage this potentially significant source of money and financial know-how? This section will attempt to answer these questions.

The OOTB Group set up the Capital Markets Mechanisms (CMM) working group to investigate whether capital markets tools could be applied to vaccine financing.[2] The working group believes that innovative financing techniques which have proven valuable in other industries may likewise generate significant progress in the world of vaccine financing. The

[1] An 'access stake' gives the investor certain rights to the technology if the firm does not provide developing countries with 'reasonable price' access to the vaccine.

[2] Group membership included several financial experts specializing in areas such as securitization and asset finance, project finance, derivatives, emerging markets and tax-exempt debt, in addition to representatives from the public sector, foundations and industry.

following are some simplified examples of how other industries use capital markets to achieve their financial and strategic objectives:

- A non-profit community hospital sells tax-exempt bonds to raise capital for the building of a new paediatrics wing. The hospital chooses tax-exempt debt – debt in which investors do not have to pay tax on interest earned – to obtain a better financing rate than they could otherwise obtain in a commercial financing arrangement.
- A developing country oil and gas company uses a project finance structure to raise capital for the construction of a new oil refinery. The company uses project finance to obtain financing terms specific to the oil refinery project – a project with a precise, identifiable, future income stream – that are better than the terms they would be able to obtain based upon the credit rating of the entire company.
- A family farmer purchases put options to guarantee a future market and hedge against the risk of low commodity prices during the next harvest. The put options secure for the farmer guaranteed prices and quantities that he can then choose to exercise or not. These options allow farmers to minimize the risks they may encounter from an uncertain market.

Overview of capital markets and capital markets mechanisms

Broadly speaking, capital markets can be thought of as the aggregation of the concepts presented in Table 1.

Fundamentally, capital markets serve to match investors' monies with those in need of financing. Capital markets mechanisms are specific financial 'arrangements' that serve to structure the channelling of monies among issuers, borrowers, investors and intermediaries.

Perhaps the most familiar examples of capital markets are the buying and selling of stocks and bonds. In the case of stocks, companies initially issue stock to raise money to be used in the business. Investors purchasing the stock are entitled to an equity (ownership) share in the business and a claim on any profits. In the case of bonds, organizations initially issue bonds to raise money, just as with stocks. However, unlike stocks, which give the investor an equity stake in the business, bonds are simply a loan from investors to the company where the bond represents the company's indebtedness to investors.

At its initial meeting, the CMM group selected a set of four capital markets concepts considered to have the greatest promise in terms of their applicability to financing vaccines or other global health product development:

- Tax-exempt debt (tax-exempt bonds)
- Securitization
- Project finance
- Put options.

Each of these concepts and the conclusions of the CMM group are reviewed in more detail below.

Tax-exempt debt

Key concept – Tax-exempt bonds: A bond issued by a municipal, county or state government (at times on behalf of non-profit corporations), whose interest payments are not subject to federal income tax (and are sometimes not subject to state or local income tax).

Key concept – Tax-exempt status: The interest income that investors receive on their municipal bond investment is exempt from federal taxation and often from state and local taxes. As a result, investors are willing to accept a lower interest rate than they would

Table 1. Elements of the capital markets

Sub-markets	Institutions	Roles	Mechanisms/Other
• Bond and fixed-income markets • Equity markets • Money markets • Foreign exchange markets • Derivatives, swaps, forwards, futures and options markets • Credit markets	• Investment and commercial banks • Insurance & and asset management companies • Stockbrokers & and securities houses	• Issuers • Borrowers • Investors • Intermediaries	• Securitization • Insurance and annuities

if their income was taxable (i.e. the non-profit corporation is able to borrow money at a lower rate).

Sample application and use of funds: Consider a scenario in which US$50 million is needed to finance the construction of a health product production facility. A PPP might work with several credit-worthy donors/investors to raise this money by issuing US$50 million worth of 10-year tax-exempt bonds. Note that for a bond to be considered for tax-exempt status, the proceeds of the bond must be used for a capital project by a recognized non-profit organization.

Source of funds: In this scenario, if the PPP were to borrow money by issuing tax-exempt bonds, it would first have to be in a position to repay both the principal and the interest to borrowers. Thus, the PPP would have to either have on hand the amount of the money it wished to borrow,[1] or have iron-clad donor commitments that could be used as collateral (see securitization below).

Evaluation: Debt, in general, enables borrowers immediately to access capital that they might otherwise only be able to access over several years. Tax-exempt debt enables borrowers to borrow this money at a rate significantly lower than standard taxable commercial rates. When contemplating investments in the order of tens or hundreds of millions of dollars, tax-exempt debt may be attractive to donors and other project sponsors if it enables them to spread a given cash commitment over a longer period of time while potentially making higher returns on their invested capital. However, ultimately tax-exempt debt is not a tool for raising new money, but rather a tool for bringing forward in time money that is already committed to – or likely to be earned by – the PPP.

Securization

Key concept – Asset securitization: A process whereby loans, receivables (i.e. expected future income) and other assets with future income streams are bundled together into interest-bearing securities.

Key concept – Asset-backed securities: A security where the promised interest and principal payments

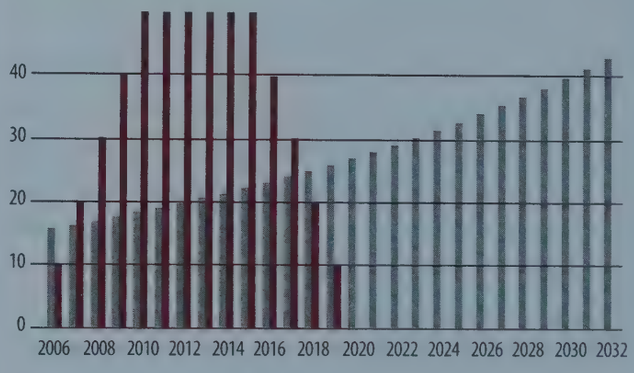
[1] Or, it would have to have the expectation of market returns that would cover development costs over time.

Gordon Brown's IFF proposal
A securitization example

In response to the September 2000 Millennium Declaration and the March 2002 Monterrey Consensus, the International Finance Facility (IFF) was proposed by Gordon Brown, the United Kingdom's chancellor of the exchequer, as an actionable funding strategy to meet the financing requirements implied by the Millennium Development Goals. The IFF proposal seeks to double current international aid flows by raising an additional US$50 billion a year.

Donors would make a series of 15-year pledges to the IFF, with each pledge being a binding commitment subject to a high-level financing conditionality (or 'a way out'). Leveraging these pledges, the IFF would securitize the donor pledges and issue bonds in its own name and thus turn the long-term income stream from donors into capital available for more immediate disbursement.

Figure 1. IFF income and disbursement patterns[1]



The facility would be replenished every three years, at which time donors would make new long-term funding pledges to the IFF as the basis for further borrowing. The IFF would be in existence for about 15 years with repayment continuing for, roughly, another 15 years after which the facility would close.

The financing profile enabled by the IFF is particularly relevant to certain front-loaded programmatic strategies currently being pursued by global health agencies such GAVI. Costly introduction periods for vaccines or drugs including introduction pricing, up-front infrastructure investment, and potential contributions to time-limited campaigns around polio and measles all may benefit from the way in which securitization makes long-term donor funding commitments available in the near term. Front-loaded financing may also enable accelerated price maturity in vaccine markets, furthering country sustainability goals.

[1] Figure 1 is taken from *International Finance Facility*, HM Treasury and the UK Department for International Development (DFID), January 2003 (available at: http://www.dfid.gov.uk/Pubs/files/International%20Finance%20Facility2003.pdf)

are backed by cash flows from an asset or portfolio of assets that generate the cash flows.

Sample application and use of funds: A group of 10 donors pledge to make annual payments to a PPP over a period of 20 years in order to fund a US$100 million, phase III clinical trial. Bundling these commitments together and selling these payment streams as securities in the capital markets would yield cash available for immediate use to fund the clinical trial over the next several years. Since the commitments originate from a variety of funders, the market would value the security based on the credit-worthiness of the underlying donors.

Source of funds: In this scenario, the original source of funds is the underlying donor commitments to the PPP. The proceeds from the sale of securities come from investors, but as with the tax-exempt debt example, all this money must be 'paid back' from the original donor commitments.

Evaluation: The basic structure of the securitization scheme has many similarities to the tax-exempt debt example – specifically, the feature of shifting money forward in time by 'borrowing' from the capital markets. The main differences, however, are that in the securitization the PPP is selling an asset as opposed to borrowing money, and since there is no tax-exempt treatment, the costs of securitization are much higher than for tax-exempt debt. The advantage of securitization is that the proceeds can be used for any purpose and are thus not limited to non-profit targeted capital projects.

Project finance

Key concept – Project finance: Non-recourse financing for a specific project in which the lender looks to the revenues the project may generate for the repayment of its loan, and the assets of the project serve as collateral for the loan (rather than the assets of the project sponsor).

Key concept – Project company: A company set up by the project sponsor(s) to own the project and raise financing (also known as a 'special purpose vehicle').

Key concept – Project sponsor: The sponsor, or sponsors, that organizes, controls and makes an equity investment in the project company. The sponsor(s) is not liable for the financial obligations of the project.

Key concept – Off-take agreement: An off-take agreement is a contract between the project company and a buyer in which the buyer agrees in advance to purchase the output of the project company's production facility.

Sample application and use of funds: Consider a PPP that is seeking to develop and introduce an affordable vaccine, drug or other health technology for developing countries. If the PPP could convince a major purchaser (e.g. UNICEF, the Pan American Health Organization (PAHO) or the Vaccine Fund) to enter into a credible off-take agreement with a PPP-sponsored project company, this project company could then raise debt and equity in capital markets based on the strength of the off-take agreement. Typically, the project company would be formed to build additional production capacity for an existing (licensed) product; however, if the off-take agreement was a 'take or pay' contract,[1] it may be possible to use project finance to coordinate funding for product development (phase III trials).

Evaluation: If purchasers and/or donors are willing (and able) to enter into an off-take agreement with a PPP-sponsored project company, the project finance structure has real potential for attracting significant amounts of new debt and/or equity financing. This structure is particularly attractive to purchasers and donors because they only spend money for the actual purchase of product (assuming there is no take or pay agreement). However, if purchasers and donors are reluctant to enter into take or pay arrangements, this tool may be relevant to projects where the risky scientific and technical stages of product development have already passed – potentially limiting its immediate usefulness product development activities.

[1] In a 'take or pay' contract, the buying party agrees to either take the product under the contract terms or pay a fee as specified in the contract. In the case of funding for product development, the buyer would thus need to be willing to make payments even in the case that the vaccine does not progress through licensure and there is no resulting product to purchase.

The International Finance Corporation: Project finance for vaccine production capacity?

The International Finance Corporation (IFC), a member of the World Bank Group, is a promising source of project finance-based funding. For example, the Vaccine Fund and UNICEF have expressed interest in obtaining vaccines that are of high quality (WHO pre-qualified) but at a lower cost (less than the price offered by the current multinational vaccine manufacturer) than are currently available. If the VF and/or UNICEF are willing to enter into a suitable off-take agreement with an emerging market vaccine supplier, it is likely that the IFC would make financing available to the manufacturer for investment in productive capacity. It is interesting to note, however, that many firms would be able to secure traditional investor financing on their own if they were able to secure a long-term purchase contract with the VF or UNICEF, and thus would not need to seek financing from the IFC. This underscores the importance of purchase agreements in causing investor monies to flow into vaccines being developed for the world's poorest countries.

Put options

Key concept – Put option: A contract that gives the holder the right to sell a certain asset to the writer of the option, at a specified price ('strike price') up to a specified date ('expiration date').

Key concept – Call option: A contract that gives the holder the right to buy a certain asset from the writer of the option, at a specified price (strike price) up to a specified date (expiration date).

Sample application and use of funds: PPPs could coordinate the sale of put options to companies that are contemplating or pursuing a specific priority drug or vaccine, such as malaria, research and development activities. Purchaser and donor partners could underwrite the options. Companies interested in pursuing a malaria product development programme could purchase put options to ensure market demand. In the event that one or more option holders do get a product licensed and produced, the option holders can 'call' their option, in which case the option writer will purchase a specified amount of product at the price specified in the option contract.

Evaluation: The main benefit in this scenario is the resulting acceleration of investment in R&D, licensure and manufacturing. Credible put options provide incentives for development without requiring cash upfront, and resources are only spent by donors or vaccine purchasers if a suitable product is developed. However, this concept is untested and the interest level of vaccine producers in uncertain. Also, this concept does not raise significant new resources for procurement if options are exercised.

Opportunity assessments for PPPs and product development

Further consideration of the four concepts presented above reveals fundamental similarities across the tax-exempt debt and the securitization concepts, and across the project finance and put options concepts.

The primary benefit of the tax-exempt debt and the securitization concepts are that they both shift money forward in time. Tax-exempt bonds enable organizations to borrow money and receive cash immediately based on their ability to repay the debt in the future. Securitization enables organizations to sell assets and receive cash immediately, provided the organization has one or more assets suitable for securitization such as a book of accounts receivables or another long-term stream of payments owed to the organization. However, in both cases the organization is leveraging existing financial resources to obtain immediate financing. Neither solution brings 'new money' to the table.

In contrast, both project finance and put options do attract 'new money'. Project finance provides a context within which both debt and equity investors have an incentive to provide financing for the project com-

Table 2. Elements of put and call options

	Buyer of option (holder)	Seller of option (writer)
Put option	Right to sell underlying asset at a pre-specified price up to a specified date	Obligation to purchase asset from option holder (if option is exercised by holder)
Call option	Right to buy underlying asset at a pre-specified price, up to a specified date	Obligation to sell asset to option holder (if option is exercised by holder)

pany; debt investors via loans to the project company and equity investors via direct ownership investment. In the case of put options, the private firms that purchase the options are motivated either to invest their own money in the project or to seek external financing from outside investors. However, the project finance concept hinges entirely on the presence of an off-take agreement, and the put-options concept can be realized only if an entity exists that is willing to guarantee the future purchase of vaccines should the option be exercised. In both of these instances, the ability to attract new money is based entirely on the premise of guaranteed future market for the product in question.

When applying the four concepts to funding phase III trials for a developing country drug or vaccine, similarities can be seen between the tax-exempt debt and the securitization concepts, and between the project finance and put options concepts.

Tax-exempt bonds and securitization may enable a PPP to transform financial resources available only over the long term into money that could be used to fund product development activities in the short term. The ability to execute a financing strategy that relies on one of these concepts is not dependent on orchestrating a guaranteed future market for the product in question. The only limitation is that in the case of tax-exempt bonds the proceeds must be used for non-profit capital projects, and thus may not be available to fund personnel, supplies, etc., to other non-capital expenses.[1]

The project finance and put options concepts do not depend on the financial strength of the PPP, but rather on the strength of the off-take agreement (project finance) or the financial strength of the put option writer. The challenge in these cases is to get investors and/or firms to invest money in a risky phase III clinical trial, even with a guaranteed market for a successful product. Traditionally, project finance investors – especially debt investors – would not accept the high levels of risk inherent in clinical trials and thus would not make the necessary investments needed to fund an expensive phase III trial. However, project finance investors would very likely be interested in providing funding for productive capacity investments for licensed products. The same basic logic applies to the holders of put options. If a firm holds enough options to guarantee a market for their product if it successfully emerges from clinical trials, it might still have difficulty attracting external investors due to the completion risks inherent to phase III trials, and may even face stiff opposition to funding the project internally if the market size is not large enough and/or the trial or product is perceived as especially risky.

From the perspective of attracting the initial financial commitment to initiate any of the four concepts mentioned above, one might expect that it would be more challenging to attract the initial financing for the tax-exempt debt and securitization scenarios. This is because for these instances, the risk of a negative outcome from the phase III trial falls to the initial donors and partners. Presumably in this scenario, a PPP could attract long-term financial commitments from donors and partners based on the prospect of using one of these financing tools to turn the long-term commitment into money available immediately to finance PD activities. Thus, the donor or partner is directly financing the PD activities, only via a commitment that is spread out over a longer term than what is actually needed to fund the trial. The essential argument made to donors and partners in this case is to convince them to fund PD activities for which there is an 'all or nothing' outcome.

Conversely, in the case of project finance or put options, the vaccine purchaser who enters into the off-take agreement or writes the put option is shielded from the risk of the clinical trial.[2] In this case, the purchaser is simply stating that they will purchase the product conditional upon the successful completion of the trial and the subsequent production of a licensed product. For purchasers such as the Vaccine Fund that exist to buy vaccines – and are interested in seeing new vaccines come to market – they might be expected to be willing participants in such a scheme.

Investors and capital markets – Conclusions

The factor underlying much of the above analysis is risk, and which parties are willing and able to bear which types of risk.

[1] Note, however, that PPPs could still pursue the use of debt through standard taxable bonds, which would not have restrictions on the use of proceeds.

[2] This assumes no take-or-pay agreement. In the case of a take-or-pay agreement, the risk of the clinical trial falls to the vaccine purchaser (the buyer in the off-take agreement).

With this in mind, perhaps the most likely outcome to emerge would be a multi-party project finance arrangement with the following characteristics:

- A vaccine or drug manufacturer sponsors a project company to pursue phase III clinical trials for the product in question.
- One or more purchasers enter into an off-take agreement with the project company in which they agree to buy 'x' million doses per year over a 'y'-year period at a price of 'p' dollars per dose.
- One or more donors would agree to 'insure' the off-take agreement and transform it into a take-or-pay contract in which the donors would be responsible for making the payments should the product not emerge successfully from trials.
- One or more investors would provide a combination of debt and or equity financing based on the strength of the take-or-pay off-take agreement.

In the above scenario, the only party bearing any significant risk is the donors. However, this may be a plausible scenario for donors if you consider that their alternative would be to fund the PD activities directly. Under the direct funding scenario, donors have a 100% probability of a cash outlay, and some unknown probability of a 'successful' outcome. In the take-or-pay scenario, donors have much reduced probability of incurring a cash outlay and the same unknown probability of a 'successful' outcome. Rationally, the take-or-pay scenario is preferable for donors; however, it may be difficult for them to get over the mindset of committing to pay only in the case of an 'unsuccessful' outcome.

Based on the above discussion, we might draw the following conclusions with regard to how best to involve specific funding sources when seeking financing from the capital markets:

- **Investors**. Investors seek to minimize the risk embedded in their future investment returns. Within the context of PD financing, the best available risk minimization strategy is to guarantee a future market for the product in question. Thus, in order to attract investor financing, it is necessary to have a purchase contract in place, which may take the form of a put option or an off-take agreement within a project finance context.
- **Health product purchasers**. Purchasers seek to minimize risk with regard to procurement. Within the context of PD financing, purchasers will prefer to enter into off-take agreements and underwrite put options as opposed to financing risky PD activities directly.
- **Donors/partners**. Although donors and partners are as focused on investment returns as are investors and purchasers, donors may be the group with the highest level of overall risk tolerance. Donors may be willing to finance product development directly – especially if they are willing to make the necessary long-term financial commitment and they find the cash-flow advantages of debt and securitization financing attractive. Donors may also be willing to assume all or some of the associated responsibilities with the roles described above for investors and purchasers.

Financing opportunity 2 – Development assistance for health

Recent estimates of additional donor resources required for development assistance for health (DAH) range from US$15 billion to US $27 billion per year. While far short of that goal, official DAH has risen from an average of US$6.7 billion in the period from 1997 to 1999 to an average of US$8.1 billion between 2000 and 2002. This upward trend has accelerated in recent years with donors making significant new commitments to the Global Fund for AIDS, TB and Malaria, the Vaccine Fund and other new structures to promote development, including two major US initiatives – the US president's new initiative for HIV/AIDS and the Millennium Challenge Account.

These funds flow through a variety of financial mechanisms including bilateral agencies (such as USAID, DFID and JICA, the Japanese International Cooperation Agency), multilateral development banks (World Bank and regional development banks), other multilateral funds and agencies including the UN system (especially WHO, UNICEF and the UN Population Fund (UNFPA)) and private foundations. The following section provides a brief overview of the DAH landscape.

Overview of development aid for health

Bilateral donors: In absolute dollar terms, the United States government is the largest single donor – accounting for between 20 and 40per cent of all DAH, followed by Japan, the United Kingdom, Germany, France and Scandinavian countries. (Note that when compared to the overall size of the US economy or the federal budget, US commitments to development lag behind most donors. The US only provides 0.1 per cent of its gross domestic product (GDP) as official aid, compared to an average of over 0.3 per cent for all donors, while the UN's stated goal is 0.7 per cent of GDP.) US bilateral funding, with the exception of commitments to the GFATM and VF, has remained relatively vertical through a range of existing and new disbursement structures – including USAID, the CDC, the NIH, and the president's new initiative on HIV/AIDS. As a result, the appropriations and administrative structures in the US are able to move resources with a great degree of donor discretion. Most European bilateral donors prioritize relatively horizontal funding mechanisms including direct budget support to countries and support for multi-donor long-term sector plans (known as sector-wide approaches, or SWAps). These European donors therefore prioritize recipient country-based resource allocation decisions and are less likely to make those decisions within central administrative processes.

UN system, including multilateral development banks: Within the UN system, DAH rose from an average of US$1.6 billion during 1997–99 to US$2 billion in 2002. Commitments from the development banks remained stationary at around US$1.4 billion. However, changes in accounting by the World Bank to include financing for health contained in non-health projects (e.g. urban, water and sanitation, budget support, etc.) suggest that its new commitments for health actually rose from around US$1 billion in 2001 to US$1.3 billion in 2002 and to US$1.7 billion in 2003. The World Bank provides country-specific support within the context of two major lending vehicles – the International Development Association (IDA) and the International Bank for Reconstruction and Development (IBRD). IDA loans, known as credits, are for low-income countries, have a 40-year repayment window and a zero-interest rate, and allow for no repayment for the first ten years. As a result, two-thirds of an IDA loan can be thought of as a grant and IDA is often the focus for providing highly subsidized lending to poor countries.

New multilateral funds: Two other important increases in DAH came from the GFATM, which committed nearly US$1 billion to disease-control projects in 2002, and from the Bill & Melinda Gates Foundation, which saw its financing for health increase from around US$450 million annually in 1997–99 to about US$600 million in 2002.

Other: Although not formally considered official development assistance (ODA), a number of international financial institutions exists that could provide project lending or credit to efforts to develop products in developing countries. The most notable is the International Finance Corporation which provides project lending to the private sector in developing countries and often serves as a lead lender. bringing in other private sector lenders with it. Other structures include the Overseas Private Investment Corporation (OPIC) and national export-import banks.

Trends and new opportunities to seek support within financing mechanisms

Support for PD activities – especially costly phase III clinical trials – clearly is not a priority for traditional development assistance financing mechanisms. Many mechanisms are driven by resource allocation decision-making and requests at the country level, and few countries (if any) will have the incentive to defray assistance today in order to invest in PD efforts that may or may not provide greater options for reducing health inequity in the future. This incentive problem has been described as an inability of the development finance architecture to provide for global or regional public goods such as breakthrough new technologies (i.e., AIDS, malaria or TB vaccines). Nevertheless, recent trends in development financing may provide a new set of options to finance product development.

Multilateral development banks, including the World Bank

Most World Bank lending – including IDA and IBRD lending – either supports country-specific projects or larger programmes (including structural adjustment and sector-wide programmes). As a result, most allocation decisions within the Bank's financial flows are

at the country level and with a combination of World Bank managers, ministries of finance and project leaders. Thus, the Bank often plays a fairly limited role in providing resources for global public goods that seem to have less direct value to countries than specific poverty alleviation projects. Furthermore, IDA and IBRD can only issue loans and credits to sovereign entities – so directly supporting commercial activities of NGO activities can be difficult.

To obtain World Bank resources for product development, PPPs must convince countries to invest their Bank resources in PD – including such activities as phase III trials. While unreasonable for many R&D activities, this approach may be possible for important burden-of-disease studies and trials for efficacy and/or effectiveness (if these phase III and IV trials are in the country in question).

The alternative approach would be to convince countries to include line items for procurement for the product in question in their sector-wide plans and health programmes. This procurement-based approach has some positive attributes. Including such line items in future sector plans indicates a willingness to introduce and use products that help convince manufacturers and international health agencies that demand – in terms of need, desire and resource availability – exists for the product once developed. Furthermore, World Bank and health procurement systems can then aggregate this future demand across countries and help support the establishment of markets for firms (including, perhaps, purchase guarantees) – potentially unlocking sources of private sector capital from the capital markets to support costly product development efforts. Finally, including these line items in future sector plans would accelerate the Bank's efforts to explore and create purchase guarantees. (The Bank is at present exploring creative strategies such as establishing 'regional' lines of credit, using IDA grants and facilitating IDA 'buy-downs' to facilitate country financing of priority vaccines. The Bank could also explore ways of using its policy dialogue with ministries of finance and health to raise the priority of immunization and vaccine financing.)

Few models exist for building this type of specific, future procurement support into development lending mechanisms. However, models such as GAVI's Accelerated Development and Introduction Plans (ADIPs) may encourage this type of support by pursuing efforts to build and solidify product demand at the national level in countries likely to be early technology adopters. But it is important to note that existing Bank instruments are not well adapted for focused, multi-country efforts such as vaccine purchase guarantees. Even if countries signalled broad commitment, simultaneously preparing and implementing projects in numerous countries might be difficult and slow. Furthermore, the countries must implement funds following the Bank's procurement requirements (including international competitive bidding), which could be a stumbling block.

One important example that could serve as a model for future global health efforts is the polio eradication initiative (PEI). Countries can submit polio eradication project applications to the World Bank for funding, and the Bank provides IDA credits to execute these projects. Once the project is complete, as documented by WHO, the country's remaining debt to the World Bank is paid for by donors through a Polio Eradication Trust Fund established at the Bank. Rotary International and the Bill & Melinda Gates Foundation have each made up to US$25 million available through the trust fund. The net result is that the programme should cost the country few resources if executed appropriately. The programme appears to be successful – with a handful of countries (including Nigeria, Pakistan and Afghanistan) taking IDA credits to help eradicate polio. A critical component to the programme's success is its 'turnkey' nature. Since the PEI can help develop a robust project plan, and since the trust fund establishes an expedited process for moving the project through Bank processes, country decision-makers and country-specific World Bank task teams find the effort appealing. Such an effort could be a model for the introduction of new products or the late stage development and testing of near-ready products in global health.

Multilateral funds and agencies

In recent years, new multilateral funds have helped mobilize interest, donor commitments and global resources to address disease or product-specific issues in global health. Two new examples, GFATM and the Vaccine Fund, are noteworthy as commitments to procure products may help developers access private sources of capital. The VF has raised over US$1.3 bil

lion in commitments to support the introduction of new and underused vaccines in nearly 75 countries. Since the Fund allows donors to pool their resources centrally for the purpose of product procurement and distribution, it is able to articulate demand to manufacturers, sign longer-term contracts and reduce market risk for industry. As a result, VF commitments may be able to drive private sector resources to PD efforts. For example, if the VF could indicate a potential willingness to procure a certain product, given some basic criteria (i.e. WHO regulatory approval), then product developers could access both public and private lending from a range of potential debt or equity investors, including the International Finance Corporation.

So far, other multilateral funds (including GFATM) have been slow to take advantage of global efficiencies in product planning, demand aggregation and strategic procurement, and therefore many new sources of potentially critical PD finance remain difficult to access. However, some signals indicate that these trends are improving. WHO has evaluated the performance of the TB drug facility and noted that centralized facilities which provide support for financing, procurement and demand management have a critical role to play in global public health. They are exploring similar efforts in other areas, including those relevant to GFATM operations.

Bilateral donors

The overwhelming trend in bilateral financing is towards direct country support and participation in SWAps and country allocation decisions. As a result, the discussion related to the World Bank above is increasingly true for bilateral donors as well. The exceptions, as noted above, remain the US and Japan where direct support from key technical agencies may continue to be a significant source of funding support.

One major new effort is worthy of discussion: the US's Millennium Challenge Account. The MCA, which will probably provide several billion dollars for development assistance, remains relatively undefined. Nevertheless, some basic principles of this new initiative are known. It will react to country proposals for funding which could include proposals from both the public sector and the private, including NGOs or perhaps commercial sector enterprises. The MCA has published a set of country criteria. Initial funding will therefore probably focus on a handful of qualifying countries with programme and planning support provided to a broader range of countries which are currently not eligible for assistance. Country-based proposals for large-scale trials or product introduction efforts would be appropriate, and the MCA is likely to accept applications directly from NGOs, PPPs and commercial enterprises.

Development aid for health – Conclusions

A review of financing opportunities within the context of development assistance for health leads to the following conclusions:

- Traditional mechanisms often fail to value and support global public goods such as product development. Nevertheless, systematically approaching major bilateral and multilateral sources of funding is critical to obtaining necessary resources.
- New financing mechanisms, whether new mechanisms at the World Bank or within the context of the MCA, represent a significant opportunity for funding.
- Understanding country systems for priority setting and developing country champions for the development and early introduction of key products represents an important step for seeking bilateral or multilateral resources. Efforts such as the ADIPs could be a model here.
- Multilateral grant funds and procurement mechanisms, such as the Vaccine Fund and perhaps a GFATM with a more centralized leadership role in commodity procurement, could help create real market demand and thereby help unlock significant project financing for product development. Leveraging these mechanisms means using the likelihood of markets (future procurement) to unlock dollars from capital markets today.

An ability to work on these four areas of resource mobilization is central to the task of raising necessary funds for product development and preparing the grounds for successful and early introduction of products.

The business case – A tool for attracting financing

The need for the business case approach

Given that investors and donors do not operate on limitless funds, both for-profit investors and not-for-profit

funders must employ business-savvy strategies to evaluate potential investments. Many investors/funders in both sectors assume a portfolio perspective, distributing their investments across multiple specific objectives, and diversifying risk/benefit relationships within those objectives. The review processes they use to evaluate applicants increasingly reflect this perspective and rely heavily on the business case model of presentation. Thus applicants seeking funding from for-profit or not-for-profit investors must become adept at presenting their proposals as business cases if they are to communicate the value of their project and funding proposal effectively.

A business case seeks to outline a specific product's ability to generate a return on investment (ROI) and to present an organized package of context, methods and analysis in support of the ROI assertions. To for-profit investors, ROI is in general a financial concept exclusively and is characterized by the total profit returned from the project in relation to the total investment made in the project. For not-for-profit funders, ROI takes on a broader meaning, but remains a concept central to the business case. For these funders, ROI is characterized in terms of total programmatic benefit in relation to the total amount invested. As regards global health, the total programmatic benefit might be measured in terms of health outcomes such as deaths averted or overall morbidity reduction, or in terms of other more intermediate programmatic objectives such progress towards product licensure or successful construction of a vaccine or drug manufacturing facility. No matter how a particular funding source defines ROI, once provided with this 'package' of information, both for-profit and not-for-profit investors/funders can readily evaluate a funding proposal based on its overall opportunity, financial soundness, proposed ROI and compatibility with the investor's particular strategy.

As potential recipients of investment funds, PPPs must develop new competencies in this business case presentation style. Armed with these tools for making business- or financial-style requests for funding, PPPs will be better equipped to apply to diverse and multiple investors and should have increasing success in obtaining funding.

This section seeks to provide a general introduction to the business case approach. First, the basic components of a business case are introduced and detailed, focusing on key items required by investors. Second, guidelines for adapting the business case format to the not-for-profit sector are delineated. Finally, an actual outline of a business case style proposal is presented in the appendix.

Components of a business case

A business case framework contains a set of criteria that enables the potential investor to make an informed investment decision. The investor wants to know two things: what is the potential return on investment; and can the project succeed in providing that return? In order to assess these questions efficiently, an effective business case-style funding proposal will contain the following components:

- a market analysis
- a project description
- a financial analysis
- a return on investment analysis.

Market analysis

The market analysis presents current market characteristics and analyses the new product's ability to perform, given those characteristics. It emphasizes the market need for the product and the product's proposed strengths.

Market characteristics: A description of the market should include its size, growth potential, competition and market segmentation:

- The size of a market, estimated by multiplying the overall quantity demand for the product by the product's proposed price.
- The growth potential of the market will be influenced by variety of factors (population growth, income growth, macro trends, etc.). If possible, market growth should be quantified.
- Discussion of the competition should include characteristics of competing products and product substitutes, and how those products compete on price, quality and other features with the main product in question. It should also review the companies that produce these competitive products.
- Market segmentation refers to the phenomenon whereby markets are divided into groups of buyers who share a similar response to a given set of mar-

keting efforts. A market analysis should describe those market segments that the new product seeks to target as potential buyers.

Product characteristics: An analysis of the product's interaction with the market should include a general product description, product characteristics that will enable it to compete and estimated market share. Features such as quality, differentiation and price influence the product's competitiveness and also determine the market share, or the product's share of the total sales within its category.

Project description

The project description should outline the process to bring the product to market. The goal of this section is to provide evidence to investors that the proposed plan has been thoughtfully developed, and is feasible and affordable. This evidence is provided through the following:

- A project outline which focuses on the who, what, where and how of each step in the process. These steps include, for example, research, development, manufacture, distribution and marketing.
- A discussion of the key risks and constraints that could threaten the project.
- A timeline with milestones, which consistently parallels the project outline.
- An introduction of the project team detailing their background and qualifications.
- A discussion of how to monitor the project and how to assess whether milestones have been attained.

Financial analysis

The financial analysis is designed to highlight the financial aspects of the project in question. Total costs and general allocation of funds should be covered in the body of the business case, while itemization of individual costs may be included in supplementary materials. Some key components of the proposal include:

- A summarized budget, including total costs of the project by major category and fiscal year.
- A proposed timetable for fund-raising and project initiation.
- Pro-forma financial statements or model, if appropriate.
- The proposed financing of the project: Currency and amounts itemized by source.
- Assessment of risks in financing that could impact project cost and ultimately profits.
- A description of current financing already obtained (if any) and its source(s).
- The share the investor will receive of the generated income.
- A thorough discussion of assumptions used in developing the analysis.

Return on investment

The ROI component synthesizes the information in the market analysis, project plan and financial proposal. The ROI part of the overall business case need not necessarily be a 'stand-alone' section, but may be included in another section as appropriate (e.g. the financial analysis).

The ROI section seeks to present a measurable expected outcome, or return, which justifies investment on the part of the investor. For example, the ROI analysis might demonstrate – based on information presented in the market, product and financial analyses – that an investment of US$25 million would be expected to return US$40 million over the following five years based on expected future sales.

Investors often perform their own sensitivity analyses that may lead to different assessments of the final ROI. It is important that the analyses presented within a business case be as transparent as possible in disclosing risks and constraints of the project and in laying out key assumptions. In summary, the ROI is only as strong as the assumptions and analysis that lead to it.

Adapting a business case for not-for-profit funders

The usefulness of the business case approach is not limited to the for-profit sector. The not-for-profit sector also seeks a return on its investment and must choose from among a variety of investment opportunities to achieve its goals. While some funders, such as the World Bank and IFC, have for years required funding applications to follow such a model, other funders such as GAVI are only now developing fund allocation frameworks that leverage the business case framework.

While a business case can be a highly effective method of applying for funds from the for-profit sector, it is necessary to tailor one's approach to a not-

for-profit framework. Such investors, by definition, define their mission and measure success using outcomes other than a purely financial ROI. Therefore, a funding proposal targeting a not-for-profit investor must begin by defining ROI in a manner consistent with the funder's programmatic goals and investment strategy. Below are some of the differences, by business case component.

Market analysis

This area, which can also be referred to as a 'problem' or 'opportunity' analysis, should focus on understanding a funder's overall goals and the product's ability to address these goals. In place of market size, other measures must be used to define the scope of the problem or opportunity. Instead of assessing the market in terms of competitors, funders are interested in assessing the available alternatives for addressing the problem. They also will evaluate product's potential for adding value to efforts in controlling the problem. Some examples might include:

- Estimates of deaths averted or other key outcomes measures.
- Current and projected burden of disease by region and demographic group.
- Current treatments available, such as mosquito nets for malaria.
- Explanation of why current treatments lack effectiveness.
- Expected impact of product on the burden of disease over time.
- Future products on the horizon and how they might mitigate impact of vaccine being developed.

Project description

There is limited need for modification of this section, since both types of funders are equally concerned with the thoroughness and feasibility of the project plan. However, one area of note for applicants for not-for-profit funding is whether the project proposal is consistent with the funder's organizational and governance context. For example, an investor may require that certain affiliated organizations be included in a scientific review panel. In such a case, the project plan and/or key personnel may need to be modified to account for such specific requirements.

Financial proposal

Adaptation of this component to the not-for-profit sector is, again, a fairly simple process. Non-profit investors want to make sure a financial plan is detailed and prudent within the context of the investor's portfolio strategy.

Return on investment

Unlike for-profit investors, who conceptualize ROI in financial terms, not-for-profit funders assess return mainly on the basis of programmatic objectives and health outcomes. In this case, it is necessary to adapt the concept of ROI accordingly, and perhaps incorporate cost-effectiveness measures to facilitate comparison with competing investment opportunities (*see* Table 3).

Business case – Conclusions

Successful for-profit private investors have become so on the basis of a sound portfolio strategy that includes a strong framework for assessing potential investments. Not-for-profit investors are increasingly adopting the business case framework to insure that they invest their limited resources in the most effective manner possible.

By using a business case model as a foundation for their funding proposals, PPPs can seek funding from a wide variety of sources, building a powerful case based on measurable outcomes for the investor. While performing the analyses required for such an approach can be at times challenging due to the difficult-to-predict nature of the market and public health outcomes, it allows applicants to present their strongest case to investors.

Table 3. Tailoring a business case for for-profit and non-profit investors

	For-profit sector	Non-profit sector
Key questions	• What is the financial ROI? • Can the project in question deliver the expected ROI?	• What is the expected benefit (cost-effectiveness) of the project? • Can the project in question deliver the expected ROI? • Does the project fit within the investor's investment strategy?
Market analysis	• Size of market (financial) • Expected market growth • Competitors, both current present and future, in the market • Expected market share of product	• Size and distribution of '"problem"' (burden of disease, etc) • Expected size of problem over time • Current Present and future alternatives to addressing problem • Expected impact of product on problem over time
Project description	• Who will run the project? • What is the action plan? • What are the risks involved in the project? • What is the timeline for the project, (includewith key milestones)? • Who will assess the project's attainment of milestones, and how?	All of the for-profit sector steps, plus: • How does the structure of the action plan fit within the organizational context and investment strategy of the funder?
Financial proposal	• Detailed budget by area and over time • Total funding requirement and expected source(s) of financing • Description of how expected income will be distributed among investors	• Detailed budget by area and over time • Total funding requirement and expected source(s) of financing
Return on investment	• What is the ROI to investors (based on expected product market share, project costs, and distribution of generated income)?	• What is the expected benefit for the investment (cost-effectiveness), based on the expected impact of the product and the overall cost of the project? • What other, non-quantifiable benefits does the project/product provide which fulfillfulfil the investment goals of the funder?

APPENDIX

International Finance Corporation funding proposal template

IFC proposal template[1]

1. **Brief description of project.**

2. **Sponsorship, management and technical assistance**
   - History and business of sponsors, including financial information.
   - Proposed management arrangements, and names and curricula vitae of managers.
   - Description of technical arrangements and other external assistance (management, production, marketing, finance, etc.).

3. **Market and sales**
   - Basic market orientation: local, national, regional or export.
   - Projected production volumes, unit prices, sales objectives and market share of proposed venture.
   - Potential users of products and distribution channels to be used. Present sources of supply for products.
   - Future competition and possibility that market may be satisfied by substitute products.
   - Tariff protection or import restrictions affecting products.
   - Critical factors that determine market potential.

4. **Technical feasibility, manpower, raw material resources and environment**
   - Brief description of manufacturing process.
   - Comments on special technical complexities and need for know-how and special skills.
   - Possible suppliers of equipment.

[1] http://www2.ifc.org/proserv/apply/proposal/proposal.html

- Availability of manpower and infrastructure (transport and communications, power, water, etc.).
- Breakdown of projected operating costs by major categories of expenditures.
- Source, cost and quality of raw material supply and relations with support industries.
- Import restrictions on required raw materials.
- Proposed plant location in relation to suppliers, markets, infrastructure and manpower.
- Proposed plant size in comparison with other known plants.
- Potential environmental issues and how these issues are addressed.

5. Investment requirements, project financing, and returns

- Estimate of total project cost, broken down into land, construction, installed equipment and working capital, indicating foreign exchange component.
- Proposed financial structure of venture, indicating expected sources and terms of equity and debt financing.
- Type of IFC financing (loan, equity, quasi-equity, a combination of financial products, etc.) and amount.
- Projected financial statement, information on profitability and return on investment.
- Critical factors determining profitability.

6. Government support and regulations

- Project in context of government economic development and investment programme.
- Specific government incentives and support available to project.
- Expected contribution of project to economic development.
- Outline of government regulations on exchange controls and conditions of capital entry and repatriation.

7. Timetable envisaged for project preparation and completion.

ANNEX 9D

Portfolio management in the pharmaceutical industry

Esther Schmid (Research Strategist, Pfizer UK)

Executive summary

Research and development (R&D) into new medicines is inherently risky. On average, only 1 in 10 new project ideas will deliver a development candidate, and only about 1 in 20 development candidates will ever reach the market as a medicine. However, not all projects carry the same level of risk, and some of these risks can be reduced with relatively small investments. The aim of portfolio management is not to eliminate risk altogether (which would be impossible anyway), but to maximize the chance of success whilst limiting costs and time.

Purpose of portfolio management

Portfolio management is a routine part of running a pharmaceutical R&D function. Senior R&D management use it on an ongoing basis to manage risk, cost and output. Key portfolio performance indicators (e.g., survival rates, numbers in stage, time to next milestone, etc.) are used both prospectively and retrospectively continually to optimize portfolio content and performance across all nine major stages of R&D. The objectives of portfolio management are threefold:

- **Risk balance**: For this, high-risk and low-risk projects are combined at required ratios
- **Maximizing the chance for a new medicine**: Depending on the overall risk profile, a smaller or larger number of projects must be included in the portfolio
- **Managing time to market**: Projects at different stages of maturity should be part of the portfolio so that failing projects can be replaced quickly.

Portfolio entry is managed by evaluating projects along key axes: commercial opportunity (based on patient numbers and medical need); technical feasibility (can potential drugs be discovered?); and development feasibility (can the hypothesis be tested at reasonable costs?).

Portfolio management in action

Risk reduction through exclusion of high-risk projects (project-specific risk)

A typical project consists of a 'drug target' (the receptor, enzyme or organism that causes disease) and associated compounds (the chemicals that interact with the drug target). Both drug targets and compounds can fail for a variety of reasons. Even a century of R&D experience has given the industry only partial insights into why projects fail, and not many of these insights have prospective value. This means that winners cannot be selected, but (some) obvious losers can be discarded (based on technical infeasibility). So even before any physical work has started, experienced drug discoverers can often decide whether a project has hardly any chance of delivering a medicine. This first-level decision removes the losers before costs are incurred (*see* Table 1). Such stratification of high-, medium- and low-risk projects can be useful for investment decisions, as well as to achieve a risk-balanced portfolio.

Table 1 only illustrates a generic methodology, which most pharmaceutical companies would follow, albeit with different degrees of granularity, weighting of factors and types of factors considered.

The projects that remain are included into the portfolio if they meet cut-off criteria for commercial and development feasibility. But they still carry both known and unknown risks regarding technical feasibility and many will be 'killed' at different stages of the R&D process. The earlier such 'kill' decisions are made, the lower the costs incurred. Most pharmaceutical companies have made significant investments in order to

Table 1. Example of risk-stratification

	Ability to provide early evidence, or existing evidence for role in human disease	Likelihood of technical success	Confidence in safety	Costs of confirmative clinical trial	Overall risk
Project 1	Low	Medium	Low	High	High
Project 2	Medium	High	Low	Medium	Medium
Project 3	High	High	Medium	Medium	Medium

acquire the necessary data for kill decisions as early as possible. Such investments include computer simulation models of compound-target interactions; acquisition and maintenance of large databases to link compound structures with toxicity problems: high-throughput screening technologies: and test-tube models, which mimic disease processes. The key aim of these large, up-front investments is to allow individual projects to accumulate more relevant information earlier in the R&D process so that informed decisions can be made at lowest possible costs. This will not always result in project termination – often the information can be used to change the chemical structure of the compounds made in order to advance along a different path.

Management of systematic risk through portfolio approach

Despite the best efforts of the pharmaceutical industry, it has recognized over the years that an undesirably large part of project risk is systematic, i.e., inherent in the R&D process. Therefore, all pharmaceutical companies, even smaller ones, use portfolios to manage systematic risk. This approach does not reduce systematic risk – rather it accepts that R&D is partly based on luck, and that many attempts are needed to achieve an overall goal. This statistical approach is used to build an optimized portfolio (in terms of the number of projects required at different stages of maturity).

Early stages need to be populated with many projects; late stages often only contain single-digit numbers of projects. Conversely, projects are 'cheap' in the early stages, whilst costs increase exponentially towards later stages. The long timelines involved in R&D mean that a sequential approach to portfolio management is rarely feasible.

Overall, active pharmaceutical portfolio management is dependent on a large 'pool' of potential and active projects at various stages in the R&D life cycle (*see* Figure 1) to allow data-driven terminations, prioritizations or accelerations. Stage gates are used as quality hurdles prior to the next (and increasingly more expensive) investment decision. As a project proceeds towards the final stages, its inherent value will increase, whilst its attrition risk will decrease. The number of projects in each stage will start to reduce with each stage, effectively producing a funnel effect, with very few, carefully selected, high-cost projects in the last stages.

Figure 1. Generic stages from idea to market

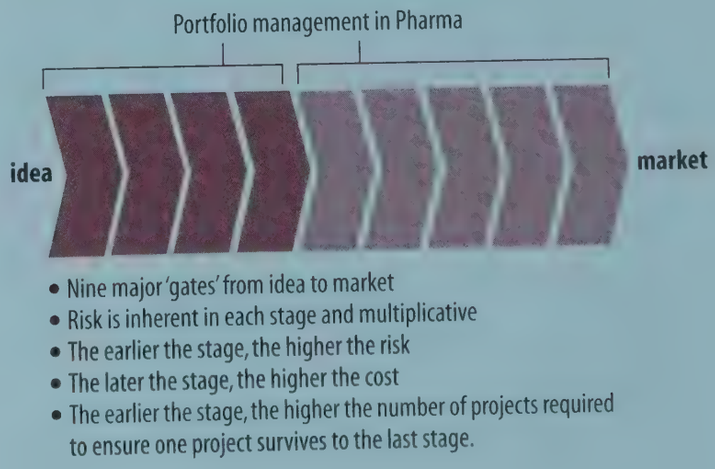


Figure 1 illustrates the need for portfolio management not only from a project-type perspective, but also from a portfolio dynamic viewpoint. From idea to market can take 10 to 15 years, which means the ability to 'parachute' later-stage projects into the portfolio can add significant value by shortening time to market, and through avoiding some of the earlier attrition stages.

Figure 2. Forecasting future output from current stage gate content in discovery

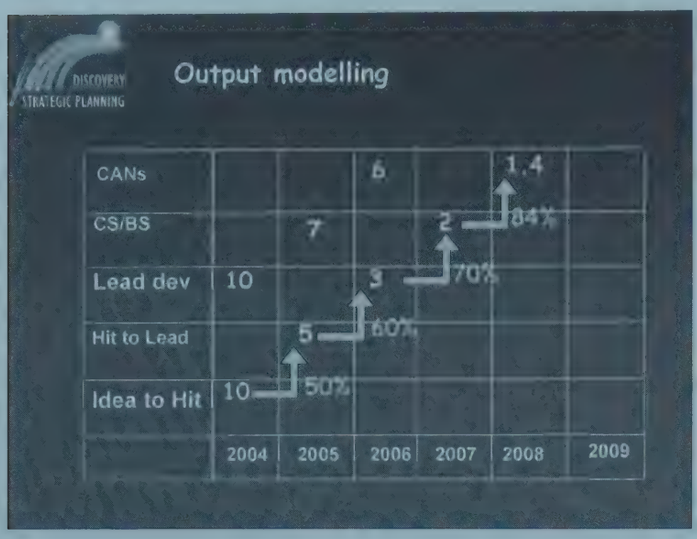


Figure 3. Forecasting future resource demands through dynamic modelling of stage gate transition

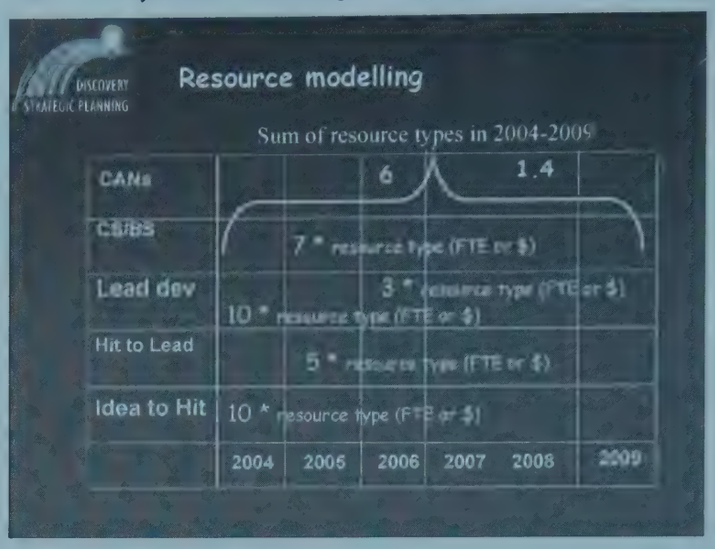


Figure 2 is only an illustration, albeit a representative one, of early attrition, and transit through stage gates. In this example, 10 new ideas, started in 2004, will only deliver five projects into the second stage within one year. Overall, it takes four years for these 10 ideas to deliver 1.4 development candidates (CANs). The probabilistic nature of this forecast means that 1.4 equates to a high likelihood of one CAN and a low likelihood of two CANs in 2008.

Figure 3 illustrates that forecasting stage content in future years from existing projects, based on survival rates allows estimation of future resource requirements. Active portfolio management will try to ensure overall stage content meets overall output goals (e.g. one product), whilst ensuring future resource demand is considered.

In summary, pharmaceutical portfolio management is vital for achieving future success. It is a complex composite of:

- Decisions on which disease areas to work in. Such decisions are based on medical need, epidemiology/demographics
- Consideration of technical feasibility
- Ongoing data collection to inform early decisions
- Costs and time required for reaching decision points
- Costs of goods (of the final product)
- Required numbers of projects in each stage and their composite risk profile commensurate with stated goals (number and types of products) and available resources.

Portfolio management is an ongoing process, requiring frequent decisions/remedial actions to create and maintain a balanced portfolio that has the highest chance of delivering against stated goals.

ANNEX 9E

Demonstrating value: Performance metrics for health product development public-private partnerships

Marc Pfitzer (Foundation Strategy Group, Switzerland)

Executive summary

A new and important type of public-private partnership (PPP) has emerged in recent years, mobilizing hundreds of millions of dollars in philanthropic and public funds to subsidize the private research and development (R&D) of new health products to cure or prevent diseases that afflict the world's poorest populations. Private firms have found that subsidized R&D can justify the development of products that bring little or no expectation of future profitability. Conversely, governments and philanthropists have found that leveraging the resources and expertise of private firms working in partnership with public and academic research institutions can accelerate drug discovery, creating a new generation of effective, affordable and patient-friendly health products that can save millions of lives.

In contrast to more immediate health interventions, however, it is extremely difficult to evaluate the effectiveness of these health product development (PD) PPPs. Inevitably, the development of new health products is a scientifically complex and lengthy process that consumes vast sums of funding and offers only uncertain prospects of success. Increasing the difficultly of evaluation, PD PPPs are merely funding intermediaries, adding a layer of overhead in channelling donor funds to targeted R&D projects. To justify their costs, PD PPPs must be able to demonstrate the value they create through easily understood metrics of performance.

Developing explicit performance metrics that go well beyond the usual reporting of dollars raised and disbursed will serve both PD PPPs and the donors that support them. Identifying and tracking the value that PD PPPs add will encourage donors to sustain their investments over the long term and, simultaneously, focus PD PPPs on the activities that are most likely to contribute to their own success.

In this paper, we propose a performance framework that goes beyond the usual measures to capture how PD PPPs create value in four ways:

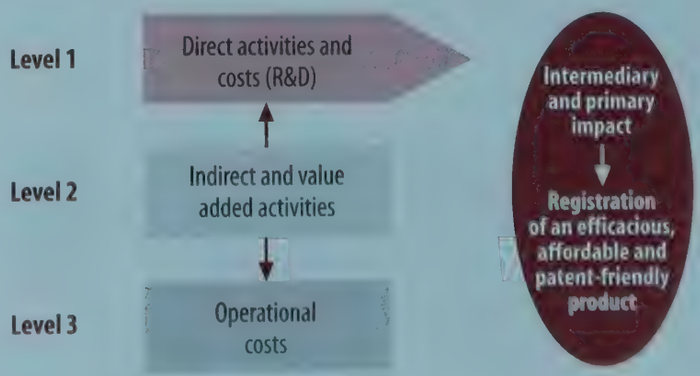
1. Building unique capabilities and platforms to attract and select the most promising projects
2. Improving their partners' research capabilities
3. Mobilizing funds in line with portfolio and organizational developments
4. Enhancing knowledge and knowledge dissemination among research partners and the broader public health actors involved in turning new products into health impact.[1]

We further seek to demonstrate the connection between these added-value activities and progress in R&D and operational costs.

Three levels to performance assessment

Donors and management can assess the performance of PD PPPs, on three levels, as shown in Figure 1.

Figure 1



[1] These four forms of value creation are derived from the *Harvard Business Review* article: "Philanthropy's New Agenda: Creating Value", by Michael E. Porter and Mark Kramer, co founders of Foundation Strategy Group.

Level 1 indicators track direct progress towards the organization's objective. In essence, this first level captures whether the PD PPPs, and particularly the R&D partners and projects directly or virtually linked to the organization, are progressing towards new products in line with expected milestones and costs.

Level 2 performance measures represent a new perspective, highlighting the PD PPPs' primary value-added activities. This is often the missing link in performance frameworks, and yet an essential one in determining whether the PDPs are successful in pursuing activities that more than justify their costs by enhancing the chances for accelerating the success of R&D efforts.

Level 3 measures assess operational costs in view of the value-added activities of the preceding level. This third level allows stakeholders to assess the PD PPPs' project-related and management overhead costs in view of the extent and value of the activities deemed necessary for success – rather than relying on arbitrary levels of 'acceptable' overhead costs.

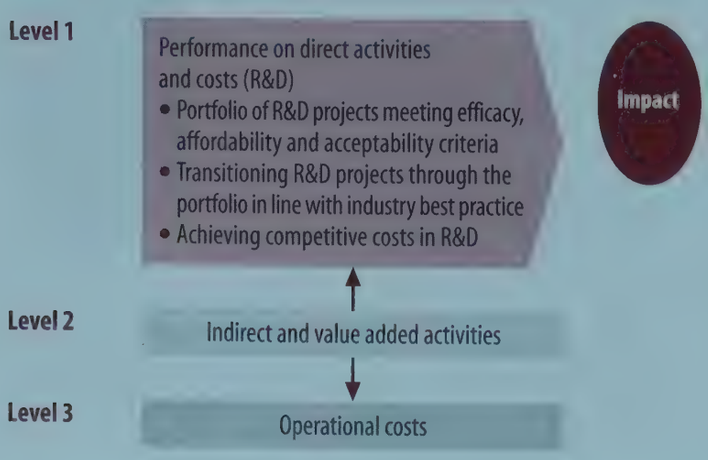
The following analysis outlines selected elements of a performance framework for PDPs, without claiming to be comprehensive for any specific organization or product.

Level 1: Performance on direct R&D activities

Developing and maintaining a portfolio of projects meeting product criteria

Based on industry experience, and knowledge of disease and product-specific attributes, PD PPPs have a good sense of how many compounds will have to be screened in early discovery phases and/or tested in subsequent development phases to succeed with at least one product registration. For new drug development, for example, the number of projects added at various stages of the portfolio versus the expected number needed to result in a final product is a key performance indicator.

Figure 2



Transitioning the R&D projects in line with industry best practices

Again, based on industry experience, PD PPPs can demonstrate that projects are (not) transitioned into the next phases of discovery and development based on best practices and on a clear expectation of how long it should take the R&D partners to complete the studies associated with each step and with the particular challenges of the target disease and product. These measures can quickly point to deviations and most importantly, to accelerated projects that are most promising

Achieving competitive costs in R&D

With an understanding of the required studies associated with each phase in the R&D process, PD PPPs should have a good sense for the cost ranges associated with each phase of each project. These figures, reported across the portfolio, will increase donors' understanding of the total direct project costs of the PD PPP, and the extent to which the PD PPP's active management has decreased R&D costs, as described more fully in Level 2, below.

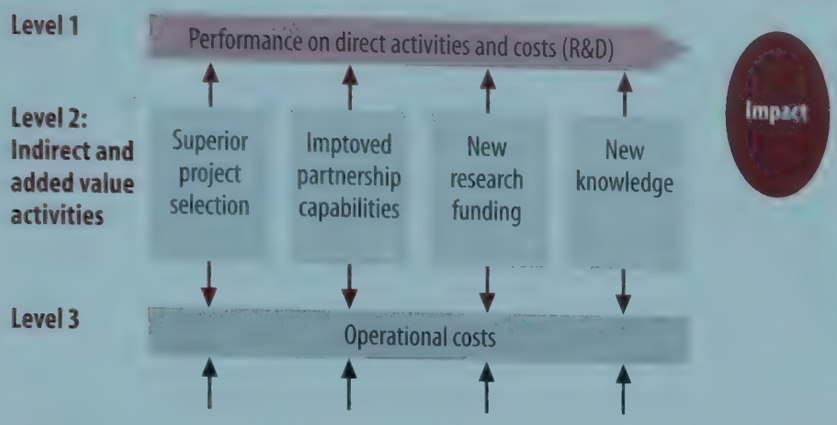
Level 2: Intermediate measures of progress on added-value activities

The direct measures of success listed above, however, still leave donors and management far short of a total performance review for PD PPPs. Equal progress on direct R&D performance indicators could have been achieved by funding projects directly, without the intermediary of a PD PPP. Performance metrics therefore must also demonstrate how the PD PPPs' specific added-value activities have contributed to the direct R&D results, as depicted in Figure 3.

Building unique capabilities and platforms to attract and select promising projects

PD PPPs can exploit their legitimacy, reach and knowledge advantages to mobilize the best projects or project elements. They are neutral, unaffected by profit mo-

Figure 3



tives, dedicated to a public health cause, offer the promise of fair contractual terms with partners in all kinds of institutions on a global scale and have access to expert advisors in their respective fields. In reporting on performance, PD PPPs can demonstrate that they are exploiting these advantages. Superior project selection is a key area of added value and one that builds on the PD PPPs' inherent advantage. Project selection in particular may create value towards adding the right number and kind of projects into the pipeline and towards creating better prospects for competitive transitioning.

Key indicators on project selection may include feedback on the profile of the PD PPP with the relevant scientific community. In turn, the number of projects proposals resulting from requests for proposals (RFPs), or even better, the number of high-quality/on-target proposals will indicate whether high awareness is converted into concrete initiatives. Additionally, feedback on the RFP and selection process may provide insight on areas for improvement.

Reporting on the time the PD PPP is taking on average to convert proposals into funded projects will point out how well a it is managing (or subcontracting), for example, the intellectual property right (IPR) process. Another early indicator of projects' potential for meeting competitive transition rates will be visible in the nature of the partnerships created. Projects that integrate teams from industry, academia and research institutes may have better access to compound screening libraries, scientific expertise, lab infrastructure, etc.

In terms of project selection, in summary, PD PPPs can demonstrate their added value by linking their activities to their reputation in their scientific community, to a continuous supply of high-quality candidates and to excellent management of the selection and contractual processes.

Improving partners' research capabilities

At the core of much of the PD PPPs' activities are those that enhance their partners' capabilities. Success on this level may particularly add value to the direct transitioning and cost measures of progress.

As part of the contractual process leading to the funding of specific projects, study guidelines, work plans and milestones are established early with the R&D partners. This process serves to focus the efforts on the desired product outcomes and sets expectations for timely delivery on the studies. The rate of fulfilment on key milestones for projects and across the portfolio is indicative of discipline towards meeting the product objectives. Indicators can point to particular studies that are being accelerated through the PD PPP's effort, as a result, for example, of securing fast-tracking conditions with regulatory authorities. Other important determinants of added value in this area may be the partners' feedback on the performance of the scientific or programme officers in contributing to their progress. Such feedback can be mirrored by the officers' own self-assessment and other important internal human resources indicators on job satisfaction, staff turnover, etc.

PD PPPs can have a tremendous influence on lowering the cost of studies through such added-value activities as outsourcing of project studies, facilitating the entry of new assets to the partnership through sharing of technologies and infrastructure or providing access to experts or compound libraries. They can also help locate clinical studies in disease-endemic countries to reinforce both the health impact and the cost objectives, and secure in-kind donations from all sectors involved (access to infrastructure, technologies, clinical trial sites, etc.). While establishing precise estimates of cost savings may prove too cumbersome, well-founded estimates can provide stakeholders with a convincing demonstration of added value.

In short, PD PPPs can demonstrate their added value in enhancing the capabilities of their partners by indicating how their activities have kept portfolio projects in line with aggressive timelines, accelerated particular

studies or R&D phases, contributed to cost reductions while maintaining a high level of satisfaction among partners.

Mobilizing funds in line with portfolio and organizational developments

Of crucial significance for all PD PPPs is the extent to which they succeed in mobilizing sufficient funds, typically from both private philanthropic and public sources, to meet the demands of the projects and of overheads. This funding gap or surplus, reported for example as a percentage of total annual needs, as in the case of Medicines for Malaria Venture (MMV), is an essential indicator of added value. PD PPPs can break down these targets by funding sources or segments, and associate fulfilment of fund-raising goals with each target segment. Backing these figures, in turn, might be feedback from donors and prospects concerning the ventures' profile, progress and so on.

In essence, the PD PPPs added value on the cost dimension is determined by their ability to close the funding gap and to demonstrate that fund-raising activities are leading to increasingly informed donors or prospects and to success with specific donor segments.

Enhancing knowledge and knowledge dissemination among research partners and the broader public health actors involved in turning new products into health impact

Knowledge development and dissemination, in the form of reports, communications and advocacy campaigns, conferences, etc., can be of substantial value towards advancing the work of all partners. Yet, linking these activities with direct measures of progress is also likely to prove the most challenging. However, PD PPPs do have a sense of – or seek to research – the major knowledge or practice gaps that are or might limit the partnerships' progress. Based on these priorities, PD PPPs should be able to report how advances in these areas are influencing both internal and partner activities. Disseminated breakthroughs on identifying biological targets may stimulate both scientists and donors, new field information on the disease burden, disseminated through the scientific community associated with the partnership, may sharpen research and development criteria. Expert additions to the scientific advisory committee may also improve project selection and review criteria, and so on.

While the focus of this paper has been on PD PPPs' core R&D activities, it is clear that knowledge activities may be most valuable upstream from R&D (for example, in informing the donor community of the extent of funding required for success), or downstream from R&D (e.g., to inform access partners of emerging breakthroughs and to begin integrating these innovations into the post-R&D delivery process) to influence all other actors involved in turning new products into health impact.

PD PPPs, in brief, can demonstrate the impact of their knowledge activities on the integration of high-quality projects into the portfolio, on sharpened R&D studies based on scientific breakthroughs, and most importantly upstream and downstream from R&D, on a better context for R&D and improved conditions for product delivery.

Level 3: operational costs

Only now can we begin to address the third level of performance around operational costs. Far too often, project overheads are evaluated on the basis of 'generally acceptable' levels. In fact, it is only with a clear sense of the nature and scope of the added-value activities performed by PD PPPs' scientific staff that stakeholders can view the direct project support with an informed eye. Reporting total project overheads (covering the scientific teams, advisory councils, R&D consultants, IPR fees, etc.) as a percentage of R&D or total costs only makes sense if put into the context of added-value activities.

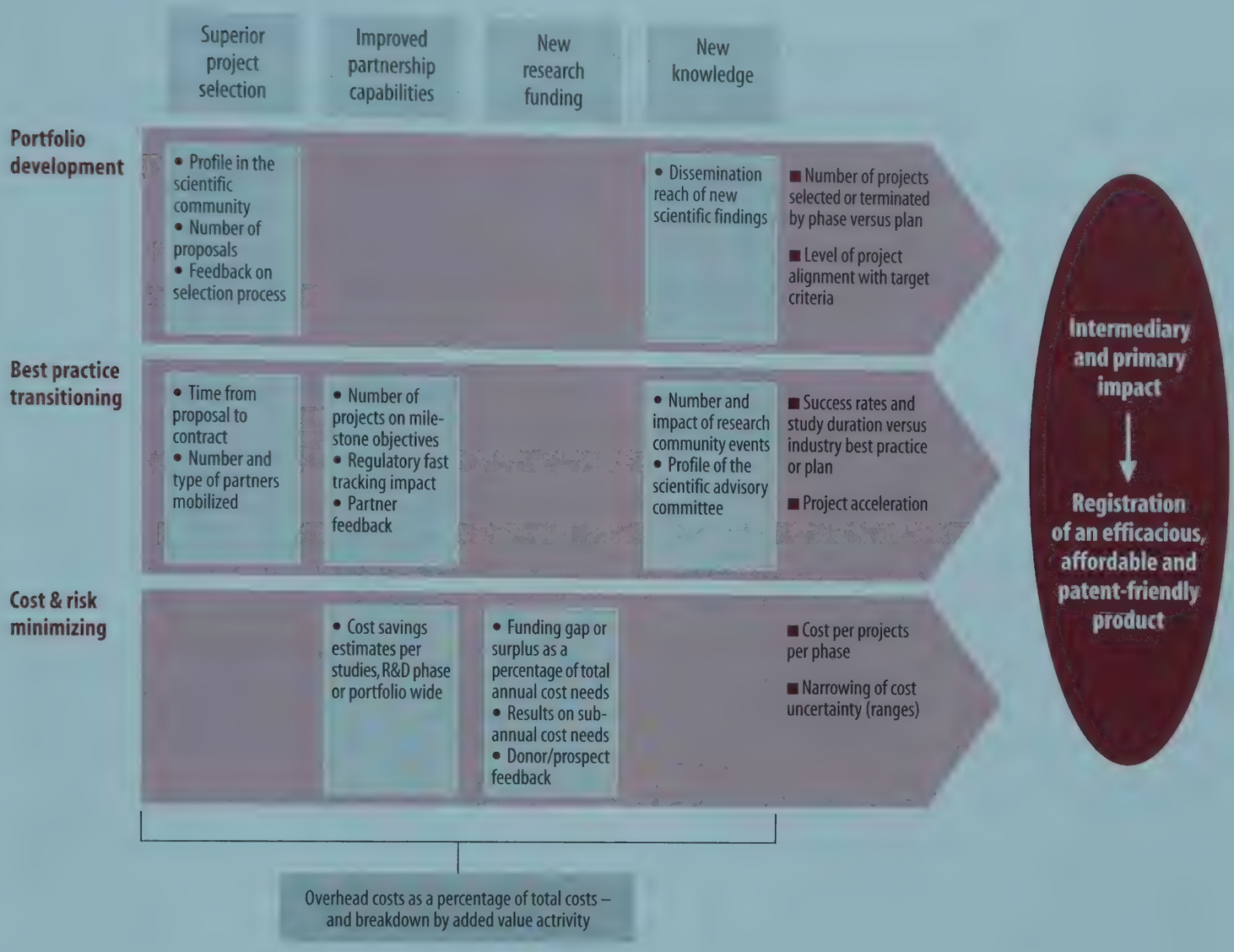
As with project-related overheads, it is only with regards to all added-value activities that the other organizational overhead costs become relevant figures. Clearly, a PD PPP with substantial fund-raising and advocacy activities will have different overhead costs than a PD PPP that is focused more on the science and management of R&D.

Summary of total performance frameworks for PD PPPs

Figure 4 summarizes select performance metrics that PD PPPs might therefore employ to demonstrate their added value and progress towards product innovations, as a basis for disease prevention or alleviation.

Clearly, for each PD PPP, whether fully focused on R&D activities or more broadly covering health access

Figure 4



issues, the relevant set of performance measures will differ. But the logic of reporting on both direct and intermediary or added-value results should not.

For all PD PPPs, demonstrating clarity of purpose through performance measures, which illustrate both the interconnectivity and added-value in their various activities, will undoubtedly contribute to their much-needed success.

ANNEX 9F

The current research-to-development 'hand-off' process for product concepts/candidate products and possible improvements in it

Solomon Nwaka (Medicines for Malaria Venture) and
Roy Widdus (Initiative on Public-Private Partnerships for Health)

Executive summary

The research-to-development transition refers to the interface between basic research and identification of pharmaceutical product concepts or leads that feed into the development pipeline. Innovative and sustainable development of pharmaceutical products for neglected diseases will increasingly depend on this interface. This discussion paper attempts to cover a perceived 'gap' and obstacles in the continuum of activities in product R&D for neglected diseases through which scientific research is ultimately applied to improve human health (*see* Figure 1).

Why the research-to-development gap is important

This particular gap is important to pharmaceutical product development public-private partnerships (PD PPPs), since they rely on a flow of product concepts from basic research. The flow that feeds their development pipeline may be insufficient if either there is inadequate funding for basic research in the relevant areas or if product concepts coming from basic research are not translated into plausible candidate products which they may then develop further. Except for a few PD PPPs that have made some investment in this high-risk area, available PD pipelines are based on identification and testing compounds from other indication areas or modification of existing compounds followed by clinical development.

The gap should also be a cause for concern for those funders whose support of basic research is driven ultimately by the desire to improve human health. If the fruits of their basic research funding are stalled by lack of attention to this gap, they are not fulfilling their mandate(s).

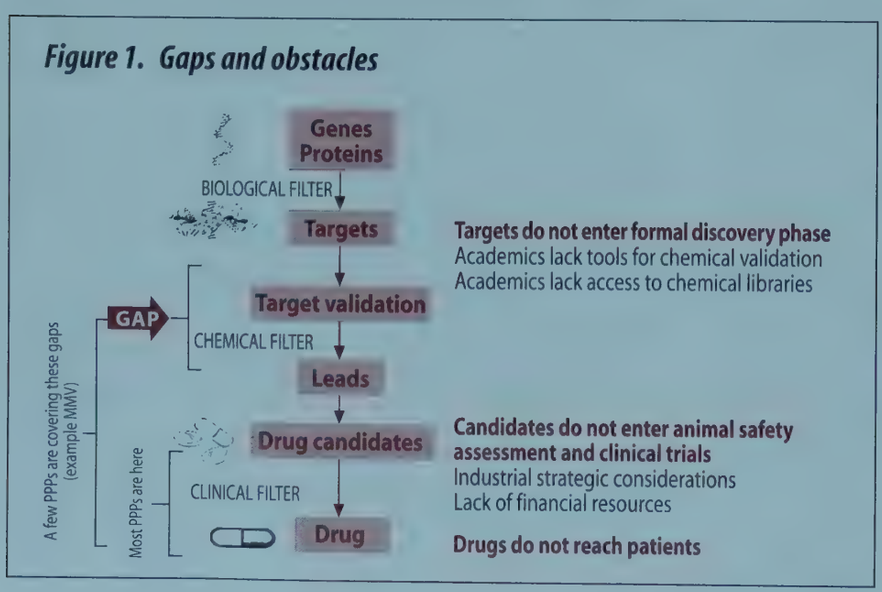
The discussion generalizes to cover the problem for all pharmaceutical health products, but readers should recognize that there are significant differences in the process for drugs and vaccines in particular.

Why the gap exists

The perceived gap in translation of product concepts into early candidate products stems from the same 'market failure' which stimulated the creation of not-for-profit PD PPPs. However, for the reasons explained below, remedying it may require interventions by actors other than the PD PPPs. Such actors include the traditional public funding agencies, academic institutions in collaboration with their technology transfer offices, philanthropic agencies supporting biomedical research, etc.

The nature of the gap can be further explained by examining the differences in involvement where a prospective commercially attractive market exists, or is absent.

Figure 1. Gaps and obstacles



The research-to-development transition where a commercially prospective market exists

- Pharmaceutical companies scan basic research and sometimes invest in specific academic research programmes to establish concept and identify leads for possible products of interest.
- Those undertaking basic research who can envisage a product with a commercially attractive market, if so inclined, can create start-up companies, often funded by venture capital or agreements with 'big pharma' to develop the product idea into a candidate product.
- These efforts are usually supported by dedicated business development units working with a clear intellectual property (IP) mandate.

These factors lead to funding and management of the research-to-development transition where some commercially attractive market exists.

The research-to-development gap where a commercially attractive market does not exist

- Pharmaceutical companies are not motivated to scan basic research or fund 'upstream' from development since they would not engage in PD due to the absence of a prospective market. Venture capital or contracts from pharmaceutical companies are unavailable to those investigators wishing to pursue product concepts arising out of basic research. Most existing PD PPPs are focused on developing the most promising candidate products available. They desire to demonstrate their effectiveness (to funders and the general public) as early as possible. Investing in early discovery concepts is unattractive because (a) the 'time to market' is likely to be very long; (b) there is a high risk of failure at these earlier stages; and (c) some available collaborators may be unfamiliar with the activities necessary for proof of concept, and may be reluctant to cede control of their 'invention' to others and to adhere to rigorous deadlines.
- Basic researchers addressing neglected diseases have fewer opportunities to feed product ideas or compounds into preliminary screening systems than for commercially attractive products. In this regard, screens recently established by NIH and under the auspices of TDR are welcome moves in the right direction. TDR is supporting whole-cell screens at the Swiss Tropical Institute, London School of Hygiene and Tropical Medicine, and at the Kitasato Institute (Japan). A screening facility against molecular targets is now in place in Harvard University (http://iccb.med.harvard.edu) and in Melbourne. The NIH is supporting a team of structural biologists in Seattle, USA.
- For leads that might be identified by industry scientists sympathetic to addressing 'neglected diseases', there is no structured system for referral (for example, scientists at a major pharmaceutical company have identified possible new agents against onchocerciasis/river blindness, but lacked a system to which to 'hand-off' these leads).
- No consistent IP strategy exists for products coming out of academic basic research.
- The limited number of R&D-capable pharmaceutical companies in low- and middle-income countries where 'neglected diseases' are endemic are unlikely to view these diseases as attractive investments, given they also desire to be profitable. These companies are happy to participate in R&D for neglected diseases but they need financial support and appropriate partnership.
- Activities that are more 'applied', particularly where they involve repetitive or routine screening, are sometimes perceived as less prestigious or innovative among academic researchers, and may not compete well for awards from basic research funders. One can argue, however, that the overlap of different technologies and expertise required for this research-to-development interface makes some of the early routine activities less obvious. Some scientific journals now emphasize applied research and product development issues. Most academics are more than willing to help fill this gap (and have expressed strong desire to do so) but funding is limiting. Typical academic funding is well suited for hypothesis-driven research but moving beyond hypothesis into application would require higher investment for proof of concept and project management. It should be mentioned that the management part of this transition is important.

How big is the problem? How should it be viewed?

These factors point to the existence of a gap and obstacle early in the research-development-utilization continuum for neglected diseases. This gap appears to be significant and could constrain the capacity of PD PPPs to be successful in the long term and be sustainable. The extent to which existing PD PPPs are being constrained by a lack of promising candidate products has not been (but should be) subject to a systematic survey. Anecdotal reports suggest it may be most severe in the uniquely tropical diseases (trypanosomiasis, Chagas disease, and leishmaniasis) and for tuberculosis.

It is possible to identify product concepts for neglected diseases that deserve more resources (e.g., alternative potentially-cheaper, protein-based pneumococcal vaccines) and technologies that might be applicable to neglected diseases (e.g., development of appropriate animal models for drugs and vaccines).

The perceived gap may not be easily quantifiable and may be better viewed as part of a continuum of activities that must function adequately for other players also to achieve success:

- Without satisfactory research-to-development handoff for neglected diseases, basic research funders with a mandate for health improvement will not achieve their mission
- Without an adequate flow of promising candidate products, PD PPPs will be forced to accept scientifically less attractive candidates, and their prospects for success will diminish
- Without earlier steps in the continuum functioning satisfactorily, those engaged in disease control programmes will lack effective tools to contribute to improving the health of populations in poorer countries
- Without adequate investment on the research-to-development interface, neglected diseases will continue to loose out from recent advances in genomics and technologies such as bioinformatics, high-throughput screening, *in silico* modelling, X-ray crystallography and the structural determination of protein-ligand complexes and combinatorial chemistry.

What actions might help close the gap

Actions that could close the research-to-development gap can be considered from four perspectives:

- Players currently operating: researchers and funders in this part of the continuum
- Establishing an understanding of the long-term implications of this gap for neglected diseases
- New funding mechanism to help fill the gap
- The current PD PPPs that are 'mid-stream' in the continuum.

Helping researchers move product concepts to candidate products

As noted above, researchers in academia and other research institutions may have difficulty in moving beyond functional hypothesis and testing their nascent product concepts such as novel compounds, potential therapeutic targets or 'designs' for vaccines.

They may also have difficulty identifying potential collaborators with expertise or skills in early product development who are interested in neglected diseases.

To ameliorate these problems, funders of various sorts could consider:

- A funding strategy that seeks to support the translation of basic research into early product leads that will feed into the development pipeline of PPPs. This would involve targeted collaboration between biologists who have the potential to identify and validate targets, structural biologists with the potential to feed structural information back into product design and chemists with access to compounds and the ability to prepare compounds that can be screened against targets and in whole cells of the disease organism. The next big step in the translation of insight gained from genomics of parasitic organisms into drug leads is to integrate compound screening and chemistry into this effort. This will form a good basis for innovative product development.
- Establishing necessary infrastructure for product concept analysis within public institutions through increased funding support.
- Increased investment in enabling technologies such as rodent models will provide early filters in progressing projects.
- Whenever possible, encourage interaction between

academic laboratories and pharmaceutical companies as complementary academic and industrial cultures are valuable in establishing product concepts.
- A strategy to integrate researchers in disease-endemic countries will help build capacity and increase their participation in supporting early product R&D which is currently lacking in most developing countries.
- The recently instituted Gates Foundation/NIH Grand Challenge programme is an important approach targeted at filling part of this gap. Encourage establishment of dedicated centres within institutions for whole-cell and target-based screens, as well as structural work to support early promising programmes.

Helping current players in the research-to-development transition contribute more effectively

Pharmaceutical companies support active networking to create links across the research-to-development gap for commercially attractive products.

Systematic linkages between basic researchers on neglected diseases and the PD PPPs interested in the same diseases have not arisen to any great extent because the PD PPPs are focused on quick results and have very limited resources for addressing such upstream, unproven ideas

Those basic researchers that are interested in verifying the potential of product concepts as potential candidate products have access to very few funding sources at present. The few PPPs that have activities in this early stage research have learnt that this area requires more resources and management to make an impact.

Hence, potential solutions include:

- Sponsoring networking between basic researchers on neglected disease and related PD PPPs. A key stone meeting held in March 2001 focusing on Drugs against tropical protozoan parasites: target selection, structural biology, and rational medicinal chemistry, and on Malaria's challenge: from infants to genomics to vaccines (*Science* 297, 343–347) is an excellent example of how networking can help to bridge this gap.
- Establishing a road map or criteria for transitioning basic research into product concepts for each disease and product area (drugs, vaccines, diagnostics).
- Increased funding for exploring the actual feasibility of product concepts.
- Helping support the establishment of infrastructure for the feasibility of product concepts in public institutions.
- Encouraging partnerships between investigators, institutions and the private sector.
- Encouraging the participation of developing countries in networking and establishment of partnerships.
- Integrating a management component to applied research.
- Defining a strategy to handle IPR coming out the programme.

Current PD PPPs

Initially it may appear as though current PD PPPs are generally best positioned to cover the process of moving product concepts from basic research to candidate products. However, this may not be practical given that most neglected diseases and their PPPs lack activity in this area.

Most existing PD PPPs have defined their tasks within the product R&D chain and have geared up with advisors and staffing accordingly. Most of them are reluctant to fund upstream for the reasons given above. Expectations for early delivery are high and funding for their chosen role is already limited. To add the responsibility for translation of basic research into candidate products would add a significant administration burden to their current tasks.

Initial lessons learned through MMV's activity in this area show that moving beyond exploratory early drug discovery research is limited by:

- Target validation, compound availability, high-throughput screening, and medicinal chemistry input
- The lack of a multidisciplinary funding strategy for projects
- New drug targets in academic labs need strong links to chemistry, high-throughput screening and management support
- Investment in enabling technologies are important for filling this gap
- Academics are willing but funding is limiting
- Early interaction between academic researchers and PD PPPs is important.

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ANNEX 9G

Ethical review capacity: Country needs, role and responsibility of partners and researchers

Rose Gana Fomban Leke (University of Yaoundé 1, Cameroon)

Executive summary

The ethics of health research in African countries has been of great concern, and increasingly deserves much attention. This is even more critical today with the increasing, devastating effects of HIV/AIDS, ongoing global interest in vaccine research and development, and advances that have and are being made in new technologies and in genomics. There is a trend for increased funding for research in Africa. The continent, with its multiplicity of endemic infections and increasing disease burden, is now fertile ground for clinical trials of drugs and candidate vaccines, and for epidemiological studies. Although there is still an absence of a research culture, the importance of health research as a tool for development is recognized. In a few countries, institutions have been set up and are now involved in health research, although their research infrastructure is weak and they lack the critical mass of trained and devoted research scientists.

Some African countries still do not have an ethical review committee (Institutional Review Board). Other countries have recently set up such a committee, but only because its establishment was a pre-requisite for a clinical trial planned for the country. Of the African ethical review committees that exist, some function well, most are mediocre, and in some countries the scientific committee does both jobs. Most members of existing committees do not have access to standard international guidelines, and have not had any training in following and interpreting them. In cases where informed consent is sought, much more awareness-raising, education and communication are needed to make the process of obtaining true consent credible.

Research, and health research in particular, is almost completely dependent on external funding due to insufficient national investment in this area. Whereas research partnerships are beneficial to both parties and to the community, and should be encouraged, collaborations sometimes lack good research practices. It is essential that those who fund and sponsor research develop real partnerships with researchers in developing countries. True partnerships will ensure all-round capacity strengthening for these developing country institutions, which will then make the most efficient use of resources to attain the objectives.

Setting up ethical review committees in African countries that do not have one is urgently needed, as is training the members of these newly established committees on the review process. Where the committees do exist, it is also important to strengthen their review-process capacity among their members. Bodies like AMANET, which is already very active in strengthening the capacity of these committees, the Pan-African Bioethics Initiative (PABIN) and the African Health Research Forum (AHRF) should be further supported in their efforts.

The ethics of health research in African countries has been of great concern, and increasingly deserves much attention. This is even more critical today with the increasing, devastating effects of HIV/AIDS, ongoing interest in vaccine research and development, and advances that have and are being made in new technologies and in genomics. There is a trend for increased funding for research in Africa and the continent, with its multiplicity of endemic infections and increasing disease burden, is now fertile ground for clinical trials of drugs and candidate vaccines, and for epidemiological studies. Although there is still an absence of a research culture, the importance of health research as a tool for development is recognized. In a few countries, institutions have been set up and are now involved in health research, although their research

infrastructure is weak and they lack the critical mass of trained and devoted research scientists.

National investment in health research is insufficient and the private sector in Africa is not involved as a partner in research funding, so institutions are completely dependent on external funding. Health research often does not address the country's priority health problems, either because research projects have not been set up by the country itself or because the research is sponsor-driven. Partnerships are rarely an association of equal parties, but rather a donor–recipient partnership. For these, and for many other, reasons, health research ethics require much more emphasis and an urgent need is seen for a valid and functional regulatory framework in each African country.

This paper will focus on some aspects of ethics in health research that need urgent attention.

Ethical review committees

Some African countries still do not have an ethical review committee (Institutional Review Board). Other countries have recently set up such a committee, but only because its establishment was a pre-requisite for a clinical trial planned for the country. Of the African ethical review committees that exist, some function well, most are mediocre, and in some countries the scientific committee does both jobs. Most members of existing committees do not have access to standard international guidelines, and have not had any training in following and interpreting them correctly. Although existing international guidelines and regulations should be considered generic, it must be emphasized that they were developed mainly by non-African nations and have not taken into consideration cultural differences that may exist.

The African Malaria Network Trust (AMANET),[1] Pan-African Bioethics Initiative (PABIN), African Health Research Forum (AHRF) and other international bodies have been involved in efforts to help strengthen capacity for health research ethics on the continent. AMANET has organized six training workshops in capacity building for African scientists in health research ethics. The National Institutes of Health, USA, has also organized similar workshops in various countries in Africa. AMANET and PABIN jointly organized one of these workshops specifically for chairpersons and secretaries/administrators of ethical committees in February 2003 in Entebbe, Uganda. Participants came from ten African countries. But the continent has 46 countries... So, many more such workshops are needed, along with a set curriculum, to ensure that committee members acquire some competence and skills to enable them to provide ethical guidance in health research in their various countries.

AMANET has also organized and run many workshops on Good Clinical Practice (GCP) for African researchers, and plans to hold more workshops in the future depending on available funding. The AHRF is working on an inventory of existing committees; it then intends to find ways of establishing them where they do not exist. Due to lack of funds, however, the project has not been able to progress as well as planned. As regards funding, it is important to note that in many countries, ethical committees cannot meet with others to review grants because members receive no funding to cover their travel costs to the proposed meeting location. In some countries, committees may be given a certain sum (about US$100) per project, but this is often not sufficient to cover transportation costs for all committee members. This lack of remuneration is demotivating for members, who may already have many other reasons to feel frustrated. The funding should be available so that members are encouraged to participate fully in these meetings.

Informed consent

Informed consent means the participants in a research project/ clinical trial have been well informed about all the advantages/risks involved in the process; that they fully understand and give their consent. In the African context, being well informed is sometimes very relative. Many participants can neither read nor write. They often do not understand English, French, Portuguese or Spanish, and so are dependent on translators/interpreters to explain the process to them; such interpretation has its own constraints. How true, therefore, is the 'informed' consent that the participant has given? Even if people living in a village where a study is to be undertaken receive a thorough explanation of the procedure and understand that consent is required, they may feel 'obliged' to give their consent because,

[1] See AMANET website: www.mnet-trust.org

given the enormous lack of medical personnel and care, they may fear that they will get 'lower-quality' treatment than those taking part in the study. So they give – perhaps half-heartedly – their consent. Getting true informed consent is not always successful, due to lack of understanding and/or education, and is a constant preoccupation. Another problem in the African context is that consent is very often required not only from the individual adult participant, but also first from the chief or village head and then the family head. If either of these people refuse, it will be difficult for the individual to consent even if he or she wishes to do so. Information, education and communication have to be greatly improved to get true informed consent.

Collaboration and partnerships

Research partnerships are beneficial to both parties and to the community and should be encouraged. Collaborating with partners, however, sometimes lacks good research practices.[1] Research should be designed to benefit the participant, the community and the nation, but this is not always the case in research partnerships. The sponsor is the donor and sets the tune. But who owns the research is not always determined. Initially, both parties should agree on – and adhere to – the terms for the collaboration. Any changes should be made only after mutual agreement. In true collaborations, the terms should include establishing in the developing country better means of communication, information and data access; authors' rights (which should be respected) and intellectual property rights (IPR) on the results of collaborative research. As regards IPR and when publishing the results of research, both parties must agree on the list of authors and the position they are allocated in the manuscript according to their contribution. Also, in true collaborations and partnerships, the financial benefits for the investigator and staff of the developing country should be looked into. It is very common to find expatriates working in a developing country on the same job as a national, but earning five to ten times more. Salaries in developing countries are very low and are the main cause of the 'brain drain' that has robbed Africa of most of its qualified scientists. The poverty of researchers, research participants and research institutions, including members of the regulatory bodies, could influence ethics review. African scientists who choose to work in their counties should be given a salary supplement, so that they can concentrate on research rather than taking on additional jobs so that they have enough money to support their families. Taking all these points into consideration when setting up a research partnership will ensure true collaboration.

Responsibility of researchers and sponsors

Many new global initiatives exist that promote health research for development. At present, they are the main bodies funding/sponsoring health research in developing countries. They are responsible for ensuring that the capacity to carry out research of local institutions is strengthened, so that they can provide service and benefits to the local community. By supporting capacity building, the sponsors would be providing, as part of the whole process, the right regulatory framework for the pursuit of health research in poorer nations.

Researchers and sponsors should make sure that a drug to be tried out in a community is one that will be beneficial to the community after the trial and also that it will be made available to the participants after a successful trial.

Accountability

The African researcher has a dual responsibility when it comes to accountability. Firstly to manage projects by accounting for all funds provided, and then to give feedback to the village or town on the results obtained by working in their community. African countries are known for their competence in mismanaging funds. So credibility in managing research funds is often questioned. African scientists therefore have the responsibility to show the world that they can be relied on as far as accounting for research funds is concerned. This is really urgently needed so that funds destined for health research on the continent can come directly and be managed by credible African research leaders and managers. AMANET is one of such bodies that is already setting the pace, and is presently funding a clinical trial in Burkina Faso, in partnership with European funding agencies.

[1] International Conference on Health Research for Development. Conference Report. Bangkok. 10–13 October 2000.

Way forward for health research ethics in Africa

There is an urgent need to locate countries in Africa with no ethics review committees.[1] Where committees exist, review process capacity needs to be strengthened, by training all members of the committee, and ensuring that they have the expertise and confidence in working efficiently as members of the review board. Some financial allocation for these committees is required for proper functioning. At the workshop hosted by AMANET and PABIN, the accreditation of these ethics review committees was discussed. While exact standards for accreditation will have to be developed, only committees that function correctly will qualify for accreditation. Standard international guidelines will also have to be adapted taking into consideration the socio-cultural differences of the continent, and in individual countries. In all of this, true success will depend on the development and sustenance of strong and durable partnerships between interested and committed parties.

A research culture is urgently needed. Education in this line must be given sufficient attention. Communities need to be educated on the importance of health research for development, as well as on the ethics of health research.

African research scientists working in Africa should use all the opportunities available to foster good ethical practices and ensure that all financial and regulatory exigencies in carrying out research projects are met.

[1] Global Forum for Health Research, Forum 6, Arusha, Tanzania. November 2002.

ANNEX 9H

Current status of clinical trials in Africa

Ebi Kimanani (International Biomedical Research in Africa [IBRIA], Kenya)
and Vaila Clements (Quintiles, USA and South Africa)

Executive summary

'Diseases of the developing world' have been the focus of increasing interest from governmental and non-governmental organizations, the pharmaceutical industry and non-profit organizations such as the International AIDS Vaccine Initiative and Medicines for Malaria Venture. A key catalyst to the non-profit efforts at bringing affordable drugs and vaccines to resource-constrained regions has been the Bill & Melinda Gates Foundation which alone has provided over US$3 billion to global health care initiatives, US$1 billion of which has been for research in infectious diseases. The United States' National Institutes of Health and the European Commission have also committed billions of dollars into research in malaria, tuberculosis (TB) and HIV/AIDS. On the industrial front, GlaxoSmithKline, Novartis and AstraZeneca are also investing both human and financial resources in these diseases.. Furthermore, there are over 300 products being developed for HIV, 45 for malaria and 22 for TB. A gap exists between products in development and the current capacity in sub-Saharan Africa for various phases of clinical trials necessary to support this product pipeline. In this paper, we review some areas of inadequacies and suggest some ways forward.

Clinical trials pipeline

In response to the global call for more attention and resources to be given to diseases of poverty, a number of organizations and pharmaceutical companies have invested resources in R&D for more medicinal products for infections endemic in developing countries. The International AIDS Vaccine Initiative (IAVI) has an ambitious goal for the decade 2000–2010: to develop up to 12 novel vaccine candidates and advance the best of them to final phase clinical trials by 2007. The Medicines for Malaria Venture (MMV) has 17 products in the discovery and development pipeline with three in exploration, four in lead identification, five in lead optimization, three in phase I and two in phase III. The Malaria Vaccine Initiative (MVI) has several development projects with a few in clinical testing stage in Africa.

These organizations have to find sites to clinically test products under regulatory and ethical requirements, find resources to manage the clinical data and provide biostatistical analysis of the data. At present, each sponsoring organization develops or finds these services independently from others with similar interests. IAVI has a vigorous site development approach starting with extensive feasibility and preparedness studies in potential testing locations. A significant portion of the activities of the Aeras Global Tuberculosis Foundation involves clinical site development designed to enhance the capabilities of physicians, scientists and public health workers in TB-endemic areas, the Western Cape region, South Africa being one example. Among testing sites for MMV products are those represented in the portfolio of programme development partners for the specific project. For the immediate needs of the sponsor organization, this solo approach to site development will serve its purpose since it is designed to optimize specific site capacities for the sponsor's needs.

However, the disadvantages to this approach include high per capita cost and potential site competition. Moreover, because such an approach primarily focuses on trial-specific requirements, more institutional-specific development issues may be overlooked, such as appropriate Institutional Review Board (IRB) overview and health authority intervention in ensuring patient safety. Most importantly, no safeguards prevent

most – if not all – of these services being contracted and dispatched to the northern hemisphere especially by organizations for whom site development may not always be a primary goal. Pharmaceutical innovator companies, for example, do not typically invest in site development, rather they will identify fully capable centres or entrust a contract research organization for their later-phase testing programme. For most of these organizations, the primary concern of product discovery and development is daunting enough without being required to take on such a significant additional responsibility as developing generic infrastructure at study locations. Therefore, the essential task of building capacity in the endemic regions to support later-phase clinical trials *per* se will be most effective if coordinated by a separate body.

The current status of clinical trials in Africa

Preliminary investigations[1] into the current status of clinical trials in Africa pointed to some priority areas that need immediate attention. These are presented below.

A framework for clinical trials exists

Health-care providers

Of the 166 health-care providers who responded to a survey on the current status of clinical research in East Africa, 68 per cent had university training in a medical or biomedical field and 32 per cent were clinical officers with certification from other medical training institutions. Clinical officers are often those in main contact with patients and in many rural areas are the sole providers of medical care. Hence, it is important to have information about these professionals, as they will be involved at some level in clinical trials whenever non-urban locations are included as research sites. Fifty-two per cent of all participants had additional training in clinical research such as good clinical practice (GCP). All respondents expressed a desire for further training in aspects of clinical trials and a strong interest in collaborating with other regional and international researchers. This availability of keen, motivated and qualified health-care professionals represents a significant advantage for those working to develop human resource and other essential systems.

Hierarchical health-care delivery systems

In most African countries, national health delivery system follows a hierarchical structure, with national referral hospitals at the top level, followed by provincial or regional hospitals, district hospitals and finally community health centres. The latter represent the first contact point with the population. In parallel to this are private health providers ranging from village home consultants to well-qualified specialist physicians , some with research experience. When setting up a clinical trial, the sponsor has to take into account the fact that the investigator site will provide basic medical care. At the same time, this provides an opportunity to use the framework for health delivery as a vehicle to install clinical trial infrastructure and systems such as regulatory and ethical review systems. Many countries such as Kenya, Uganda, Tanzania, Nigeria and others are indeed using this structure to institute national ethical review committees and research guidelines. Protocols approved at the national level can be conducted in any of the hospitals or clinics at the lower strata.

Research networks

Research networks are a collection of sites in various countries with a common function. One example is the African Malaria Network Trust (AMANET), which is a collection of about 30 institutions in 20 countries all carrying out some level of malaria research (*see* Appendix 1, Figure 1 for locations of sites and Table 1 for key to the map). Collectively, the network has about 600 scientists at undergraduate, doctoral and physician level, 70 per cent of whom are nationals. It has basic and non-uniformly distributed equipment and minimal experience with clinical trials. However, the network is keen to enhance the collective infrastructure for clinical trials in order to meet a significant portion of the looming demand for sites as adhered to in the introduction.

Another major research network is INDEPTH with about 30 sites in 16 countries involved in long-term intensive demographic surveillance systems (DSS). By their very existence and access to a rich base of longitudinal population data through their communities, all INDEPTH sites have basic infrastructure and a high

[1] Kimanani EK. Good Clinical Practice in East Africa: Call for a regionally harmonized ICH GCP guideline. *East African Medical Journal*, October 2001, pp549–554.

potential for clinical trials. In particular, the network has tremendous marketable resources for clinical trials, namely, access to participants in highly malaria, tuberculosis and HIV/AIDS endemic communities. The network is in the process of developing a health intervention platform, which will primarily focus on assessing and classifying sites, developing the capacity and brokering for clinical trials for member sites. In their initial phase of this platform, 10 INDEPTH sites have expressed an interest and are actively working on the platform for the network. These have been indicated in Figure 1 and Table 1 in Appendix A.

In summary, while a skeleton framework for clinical research exists, it must be noted that much of the research conducted to date has been either academic-driven projects or epidemiological surveys, few of which have been run to serve a regulatory purpose. The focus of future research projects needs to be undertaken within the framework of product license applications to regulatory health authorities.

Political will towards clinical trials exists but is distracted

Governments in the region have shown initiative towards promoting clinical research by setting up research institutions with the general mandate to carry out medical research to influence public policy. Examples of these institutions are the National Institute for Medical Research in Tanzania, the Joint Clinical Research Center in Uganda, the Kenya Medical Research Institute in Kenya and the National Institute for Pharmaceutical Research in Nigeria. These institutions have been responsible for raising the general public's awareness of the advantages of clinical research, for providing venues for local scientists to pursue clinical research investigations and for influencing public policy to some extent. More significantly, African leaders have pledged their political will and platforms for promoting and creating social, political and economic environments which can boost creativity and support all efforts to alleviate poverty. Health in general and in particular, creative initiatives and research activities targeting the three leading killer diseases, HIV/AIDS, malaria and TB, have been identified as priorities. A commitment has been made in the New Partnership for Africa's Development (NEPAD)[1] manifesto for individuals and groups to come up with ideas and ways for research into the alleviation of these diseases.

Non-urban areas are isolated

Medical practitioners in remote areas who have the potential and are keen to enter into the field of clinical investigation feel isolated from the core of clinical research, facilities, funding and decision-making. According to such practitioners, almost all clinical studies carried out in their countries take place in just one or two institutions usually located close to the national capital. While these experienced sites run the risk of being overwhelmed, the potential of more remote areas remains untapped. In these areas, patient populations have little or no access to care and attention and would therefore be desirable for clinical studies because they are treatment-naive. Moreover, there is a need to expand clinical research infrastructure beyond existing, experienced institutions.

Inadequate facilities

Facilities for handling and managing clinical trial data are minimal at best, especially relative to global standards. When they exist, subject screening tools, facilities and biological sample handling laboratories are limited to research institutions (usually no more than one in each country), medical training institutions hospitals (at most three per country) and national hospitals (again usually one per country). Data processing and reporting are almost entirely handled by the sponsor, typically from outside the continent.

Inadequate travel and communication infrastructure

Logistics involved in conducting clinical trials in several sites in the region present difficulties, but these can be overcome. As in most developing countries, transportation and communication issues remain challenging. However, there are good air connections between major international cities, although travel by air is less dependable within each country. Roads to most of the remote areas are good enough for a reliable vehicle. Communication in most areas is possible by cellular phones. The pledge of government leaders to support clinical research in general will help to create logistically viable environments.

[1] The New Partnership for Africa's Development (NEPAD). *The first core document*, 2001. http://www.touchtech.biz/nepad/files/en.html

Significance of cultural factors

Cultural factors are still significant issues to be considered when planning and conducting clinical trials in Africa. As long as a study is seen to be from the 'outside', acceptance and cooperation may not be as forthcoming as may seem on the surface. Site development covers a multitude of activities, the basic foundation for which needs to comprise social and ethical acceptance that clinical trials are positive for the people. Health-care clinics, local religious and community leaders, etc., need to give studies a favourable reception for such acceptance to be forthcoming. So, essential systems should be built from the ground up, allowing enough time for the systems to be rooted in goodwill and earn the trust of all local players. Community Advisory Boards (CABs) are a good start in this regard. Their role is to promote communication between the sponsor, the research team and the community of trial participants and ensure that community leaders are informed about the protocol, buy in to the trial and help with logistics and follow-up of the study.

Dependency on outside funding

Current methods of sponsoring studies do not foster self-sufficiency and capacity building. The reasons are multi-factorial but may be largely due to the lack of indigenous drug development, lack of financial resources, insufficient political support and unclearly communicated missions and motives of the sponsors. Including Africa as an authentically feasible, viable and sustainable partner in global drug development has many significant advantages that may not be immediately monetary. Articulating these advantages and building capacity to support later-phase clinical trials would best be fostered by an independent organization situated in Africa which has credibility on both local and international fronts. The role of such an organization would be to serve as a link between African institutions and the affected people, and the clinical trial sponsors with sustainable milestones on local self-sufficiency.

Way forward

What targets do we set?

In order to meet the prospective demand for clinical trial capacity it is necessary to set some targets. The most basic and achievable targets for the next decade are, for example:

- Regionally harmonized clinical trial guidelines
- International Conference on Harmonization (ICH) compliant IRBs to ensure both ethical and safe clinical research in a number of African countries
- Clear accessible health research requirements based on regulations
- A threshold level (say 50 per cent) of local capacity to support a wide range of clinical trials.

How do we get there?

The workshop on clinical trials capacity in low- and middle-income countries[1] highlighted some areas that need urgent attention and outlined some minimum requirements for an entity such as proposed above. Briefly, these are presented below.

- Building infrastructure and capacity for clinical trials is a multifaceted and expensive challenge but absolutely essential. Hence most urgent is the call for leadership in capacity strengthening.
- Committed and compassionate scientific and political leaders are needed in order to advocate for and manage clinical trials.
- Material and financial support will be needed to enhance basic infrastructure, general training of clinical trial support personnel with particular attention to GCP and publicity of research sites through, for example, a regularly updated database of clinical trial investigators and sites, preferably Internet based.
- Investigators and research sites will need to work on research governance structures.
- This means entering into dialogue with the right government offices that regulate clinical trials so that these are communicated clearly to those that are involved in clinical research. It also means instituting scientific and ethical review committees according to local and international regulations is critical.
- There needs to be relevant, self-regulating and adaptable systems for administration, project management, study conduct and site audit.

[1] *Clinical trials capacity in low- and middle-income countries: Experiences, lessons learned and priorities for strengthening*, Meeting Report by the Initiative for Public-Private Partnerships for Health, 2004. http://www.ippph.org.

Recommendations

We end this paper with two recommendations to be considered by PD PPPs and funders.

- Many components for clinical trial support and facilitation are common to multiple disease areas and their interventions. It would be worthwhile for PD PPPs to consider some common platforms for building the capacity to realize these cross cutting capacities.
- We feel that for many reasons such as those discussed above, PD PPPs' African partners should spearhead clinical trial facilitation in Africa.

Acknowledgements

We are grateful to Roy Widdus for providing the direction for this paper. Discussions with Dr Chris Webber, MD, Dr Willie Conradie, MD, Ms Sorika Vannieker and Dr Annalene Nel of Quintiles provided a useful contract research perspective in site development.

APPENDIX A

Figure 1. Location of INDEPTH (DSS) and AMANET (malaria) sites in Africa

Table 1. Names of sites shown in Figure 1

Key	Country	Site	Network	Remarks
1.	Senegal	Institut Français de Recherche Scientifique pour le Développement en Coopération, Centre ORSTM de Dakar	AMANET	Malaria
2.	The Gambia	Medical Research Council Laboratories, Basse Field Station	AMANET	Malaria
		Medical Research Council Laboratories, Fajara		
		Farafenni	INDEPTH	Farafenni is a small town on the north bank of the The Gambia River about 170 km from the capital Banjul. The surveillance site is located in a rural area and comprises 40 small villages.
3.	Côte d'Ivoire	Pierre Richet Institute	AMANET	
4.	Burkina Faso	Centre National de Lutte contre le Paludisme (CNLP) Muraz Centre	AMANET	Malaria
		Centre de Recherche en Santé de Nouna (CRSN)	INDEPTH	CRSN is located in the Nouna health district in north-western of Burkina Faso. The research area includes about 55 000 inhabitants settled over 1 175 square km.
5.	Togo	National Malaria Control Program, Ministry of Health	AMANET	
6.	Benin	Regional Center for Entomological Researches of Cotonou	AMANET	

Table 1. Continued

7.	Nigeria	Cellular Parasitology Program, Ministry of Health	AMANET	
8.	Niger	Research Center for Meningitis and Schistosomiasis	AMANET	
9.	Cameroon	Organisation de Coordination pour la Lutte contre les Endemies en Afrique Centrale (OCEAC)	AMANET	
10.	Gabon	Centre International de Recherches Médicale de Franceville (CIRM)	AMANET	
11.	Ghana	Navrongo Health Research Centre	AMANET INDEPTH	
12.	Sudan	Blue Nile Research and Training Institute (BNRTI)	AMANET	
13.	Ethiopia	Jimma Institute of Health Sciences	AMANET	
		Butajira	INDEPTH	The DSS was started in 1987 with a population of 28 000, which has now grown to over 41 000.
14.	Uganda	Med Biotech Laboratories	AMANET	
		Rakai	INDEPTH	The Rakai project is situated in the Rakai district in south-western Uganda. The DSS covers 320 square km and a population of about 45 200.
15.	Kenya	Kenya Medical Research Institute, Kilifi Unit	AMANET	
16.	Tanzania	Amani Medical Research Centre	AMANET	
		Institute of Public Health	AMANET	
		Magu	INDEPTH	Magu is located in Magu district, in Mwanza region of north-western Tanzania. The DSS area covers 6 six villages.
		Ifakara Health Research and Development Centre	AMANET INDEPTH	Ifakara's DSS includes 25 villages of in Kilombero and Ulanga districts, in Morogoro region in, south-western Tanzania with a population of about 67 000.
17.	Mozambique	Instituto Nacional de Saude	AMANET	
		Manhica	INDEPTH	Manhica site is located in Maputo province in southern Mozambique. The DSS population is about 62 000.
18.	Zimbabwe	Blair Research Institute	AMANET	
19.	Zambia	Tropical Disease Research Centre	AMANET	
20.	South Africa	National Malaria Research Program, Medical Research program	AMANET	
		Agincourt	INDEPTH	Agincourt is located 500 km nNorth-east of Johannesburg in the Bushbuck region. The DSS covers 21 villages with a population of about 67 000.
		Africa Centre	INDEPTH	This DSS is located in northern KwaZulu-Natal, South Africa with a population of about 11 000 households.
21.	Guinea Bissau	Bandim	INDEPTH	The study area comprises five suburbs of the capital and a mobile rural unit. It covers a population of about 100 000 inhabitants.

ANNEX 9I

Emerging lessons in preparing for uptake of new vaccines

Gargee Ghosh (Center for Global Development, USA)[1]

Executive summary

Public-private partnerships (PPPs) are a potentially 'win-win' approach to speeding the availability of new products for the poorest of the poor. They help mitigate industry's risks associated with commercial investment in global health products in exchange for accelerating development and/or securing access. Many of today's PPPs see the most direct route to this goal as mitigating upstream risks for biotechnology or pharmaceutical companies by providing direct 'push' funding for scientific research, clinical trials or licensure; as such they are focused on funding and managing increasingly complex product development (PD) portfolios. But in this exclusive (or overwhelming) focus on PD, PPPs may be defining their mission too narrowly and in a sense not preparing for their own success – adequate plans will not be in place for what to do when a product becomes available. Instead, PPPs should develop a parallel track of thinking and preparing for introduction, starting today. This parallel agenda should be part of the strategic plan for all PPPs involved in new product development, but will become increasingly important (and urgent) as a product emerges in the development pipeline.

The vaccine world is on a learning curve when it comes to preparing for the introduction of new products. Its recent and current efforts may offer some lessons for PPPs involved in the development of a wide range of global health products. The historical approach to developing an introduction strategy has been to start thinking about it only after the product is available. A hepatitis B (HepB) vaccine was introduced in the developing world in the late 1980s, nearly 10 years after the developed world; the vaccine for haemophilus influenza type b (Hib) has a similar story. By 2001, 126 countries had introduced HepB vaccine; only 77 countries had introduced Hib. The cost of this approach has been estimated in hundreds of thousands of preventable deaths.[2]

Current attempts to prepare for introduction of a Meningococcal conjugate vaccine, an HIV vaccine, rotavirus and pneumococcal conjugate vaccines use different approaches, but all attempt to create and signal credibly more predictable demand[3] for vaccines before (sometimes long before) products are ready for market. These PPPs hope that enhancing demand will influence not only the timing and rate of uptake once a product is available, but also the suitability of the product being supplied (e.g. profile, price) and the supplier landscape itself (e.g. number of firms, developed versus emerging suppliers).

Other initiatives in the vaccine community, such as the Pull Mechanisms Working Group, may offer additional demand-creation tools for PPPs to incorporate in their strategies. By guaranteeing financing for a product not yet on the market, pull contracts may mitigate downstream market risk to encourage PD and assure supply.

Emerging lessons for today's PPPs are both intuitive and important. A product introduction strategy is a critical part of a product development strategy. Lack of the first may actually inhibit the latter, so planning for introduction must begin early. Planning for introduction is not just about understanding epidemiologi-

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[2] GAVI estimates that in 2001, 521,000 people died of HepB and 450,000 died of Hib. See GAVI website www.vaccinealliance.org

[3] Demand in the case of vaccines incorporates willingness to use with ability to use and ability to pay (or find funding). From telephone conversation with Alan Brooks.

cal need; it requires an integrated package of activities including demand creation through marketing, communication and education; credible demand estimation; financial planning; and procurement strategies. These activities must be undertaken with an eye on the long-term objective – product introduction is not a goal in itself, but must be done as a first step to achieving sustainable public health impact in a mature market. PPPs are well placed to play a critical role in this work – they should already embody global expertise and energy around a particular effort. But PPPs today do not necessarily have the right skills – or budget – in place to take on this task. Preparing for uptake requires a different set of skills than product development portfolio managers; expertise analogous to a commercial product launch team must be built to complement existing skills and be dedicated to the task. And no matter what their internal capacity, PPPs cannot do this alone – they must in the end motivate others to act as well.

Preparing for uptake is a significant task to place on the shoulders of already overburdened PPPs. Even in the best of circumstances with all resources in place, bringing new products to market is a risky business. For public goods like vaccines, in resource-poor developing countries with shifting priorities and political tradeoffs, and with complex public sector donors, the task is all the more difficult. But preparing for introduction is central to the ultimate success of the PPPs' enterprise and far too important to be ignored any longer.

This paper is divided into three sections:

- Defining the problem
- Approaches to the solution
- Emerging lessons.

Defining the problem

Despite all evidence pointing to their life-saving power and their overwhelming cost-effectiveness, vaccines are often not used to the extent they could be in the developing world, are not supplied to the extent they are needed or are not even created in a form that meets the needs of those who need them most.

Why is the vaccine market failing the developing world? Vaccines are extremely risky and costly to make, and commercial suppliers often see developing world vaccine markets as high-risk and low-reward because demand is unpredictable and prices are low.[1]

For mature vaccines, demand can be unpredictable as need, distribution capabilities and national priorities change. Uptake of new vaccines can be slower than anticipated if individuals and governments do not understand the benefits of vaccination in general, let alone the value of a particular vaccine. This results in forecasts and procurement awards that can be wildly different from actual offtake.[2]

For all vaccines, the ability to pay is an overwhelming constraint on market demand. Traditional vaccines – like diphtheria-tetanus-pertussis (DTP) combinations – sell for very little per dose, and until recently there had been little reason to think that would change for new vaccines.[3] The existence of the Global Alliance for Vaccines and Immunization (GAVI) and the Vaccine Fund (VF) creates an important opportunity to work with industry in a new way, but this opportunity has not yet been fully tapped.

In this context, PPPs charged with the mission of reducing burden of disease in a neglected area face a complex challenge. PD is critical, but it is not enough. Product development without a parallel plan for unlocking some of the constraints on demand (ability to use, willingness to use and ability to pay) has critical consequences. When a product is available, years can be lost developing, negotiating and financing a strategy. The opportunity to save lives is wasted during that time. But there is another important 'trickle-up' effect. From industry's perspective, the lack of a public sector introduction strategy, in a world where donor-financed procurement will make or break the

[1] While margins may vary across developing world vaccine products, revenue opportunity as a whole is minimal. Vaccine revenues amount to only 1.5 per cent of global pharmaceutical sales, and are roughly equivalent to annual sales of single blockbuster drugs such as Lipitor or Prilosec. Of 2000 vaccine sales, low-income countries consumed nearly 50 per cent of doses (approximately 2.5 billion) but contributed only 3.3 per cent of revenue (US$250 million).

[2] In 2001, GAVI purchased 18 per cent per cent of the doses it awarded for combination vaccines; for monovalent Hepatitis B, offtake in 2001 was only 11 per cent per cent of the award. For further details, see Mercer Management Consulting, 2002.

[3] Average UNICEF procurement prices for Diptheris-tetanus and whole cell pertussis (DTPw) vaccine were well under US$0.10 per dose throughout the 1990s. Since 1998, the price of DTPw has actually been increasing – from US$0.06 per dose in 1998 to approximately US$0.09 in 2003. See Global Alliance for Vaccines and Immunization, 2001.

market, means there is no credible information available about the market in advance – no insight on market size, price or predictions about market maturity. In short, industry is left without the critical pieces of information on which it usually bases production, commercialization and even earlier research allocation decisions.[1] This makes the developing world an extremely risky market – one that may not offer sufficient reward to justify the risks of engagement. The results of this uncovered risk – as we have seen in the 10/90 gap and in the pipeline of products being developed[2] – is that the developing world is relegated to receiving cast-off products from industrialized markets, or even worse that industry is deterred from playing in developing country markets at all. And this, in turn, makes the product development goals of the PPPs much harder today.

Approaches to the solution

Recent efforts

The hepatitis B (HepB) experience

Merck introduced a plasma-derived hepatitis B vaccine in the developed world in 1981, at a price of about US$30 per dose or nearly US$100 for the complete series of three shots. The vaccine used a chemical purification technology that resulted in a high-quality but high-cost product, specifically targeted to health workers and other high-risk individuals in industrialized countries. "Only after the companies were successful at producing such a Hepatitis B vaccine did they realize that the real need was not in the West but in the countries of Asia and Africa" (*Asian Development Bank, 2001*).

In 1986, several HepB experts formed the International Task Force on Hepatitis Immunization with the goal of creating supply and making the case for integration of a HepB vaccine in the developing world. The task force's primary objectives were to lower the price of the vaccine by transferring technology to lower-cost producers and to convince developing countries and the international health community that HepB control through immunization of infants should be a top priority.

The use of pilot projects in developing countries was central to the task force's efforts, to prove that the product could be successfully integrated into immunization programs with positive results. These demonstration projects would prove to countries that HepB immunization was both possible and worth doing and prove to industry that demand could exist at the right price, in the hope of creating incentives to supply at that price.

In 1987, the task force designed and piloted its first project in Lombok, Indonesia. They solicited international tenders for supply of the vaccine; the tender required that bidders offer Indonesia the same price once it introduced the vaccine nationwide and offer the same price to other developing countries. The winner was the Korean Green Cross, which, capitalizing on advances in lower-cost production technology, offered to supply the vaccine at US$0.95 per dose, i.e. much lower than the prevailing market rate of US$15–30 per dose.

This low price fundamentally changed the nature of the HepB market. Through the late 1980s further demonstration projects followed, and the task force provided assistance to several countries developing international tenders. By 1992 a number of Asian countries, including China, Thailand, Indonesia, the Philippines and Mongolia, had introduced HepB into their routine immunization programmes. The price dropped as low as US$0.65 per dose in 1991.

In parallel, Merck and SmithKline Beecham introduced a recombinant DNA vaccine in the late 1990s at a price of about US$40 per dose. Competition with the plasma-derived vaccine drove prices down, and developing country manufacturers also began to supply low-income markets at drastically lower prices. Prices dropped to just over US$1 per dose for the recombinant product by the early 1990s.

In 1992, WHO recommended that all countries incorporate hepatitis B into their routine immunization schedules by 1997. Since then, price has contin-

[1] While guaranteed information is obviously not available in developed world markets, biotechs and pharmaceutical companies are able to make market estimations based on assessments of need and willingness to pay. This market analysis is a critical part of 'go/no-go' decisions during the PD and pre-launch phases.

[2] Less than 10 per cent of the amount spent worldwide on heath research and development is devoted to the major health problems of 90 per cent of the world's population. The impact of this has been clear in new drug development: of 1 233 drugs licensed worldwide between 1975 and 1997, only 13 were for tropical diseases (and only four of those were developed by commercial pharmaceutical companies specifically for civilian human populations). See Institute of Medicine, 2003.

ued to be a major barrier to the introduction of HepB vaccine in the developing world (even at US$0.30 per dose for the monovalent vaccine, it was three-to-five times more expensive than older vaccines like DTP and measles[1]). Still, the availability of a low-cost supply has kept the price decreasing and the market reasonably robust; more recent support from GAVI and the Vaccine Fund has accelerated introduction in many of the world's poorest countries. As of 2001, nearly 100 countries provide the HepB vaccine as part of their routine campaigns, but more than 60 per cent of the world's children[2] – mainly the poorest of the poor – had still not received this potentially life-saving vaccine (Widdus, 2000 and WHO, 2003).

From the time a hepatitis B vaccine was available on the market, it took five years to begin a concerted global effort to bring the vaccine to the developing world; 10 years to reach even double-digit coverage in South-East Asia; and 11 years to convince WHO to make a universal recommendation for use. This lag in introduction and uptake is completely unacceptable when it means five, 10 or 11 years of lives lost. The public sector and the developing world were almost caught by surprise with the availability of this effective but expensive vaccine, and had to start from scratch in 1981 by creating both supply and market demand. HepB can be seen as a success story in some sense – prices did drop and the product was introduced with some success – but it is a story that leaves room for improvement.

The haemophilus influenzae type b (Hib) experience

Since the late 1980s, highly effective vaccines against Hib have been licensed and widely used in the industrialized world.[3] The effect has been dramatic – incidence of invasive Hib disease has fallen by more than 90 per cent in those countries. Yet in the developing world, Hib runs almost unchecked as very few countries use these vaccines in routine immunizations. In 2001, only 77 countries of WHO's 191 member states had even introduced Hib vaccine, and most of this figure represents introduction in North America, Europe and Latin America. The vast majority of countries in South-East Asia and Africa have still not introduced the vaccine.

Cost is commonly cited as a significant barrier to the introduction of Hib vaccine. Even at the price in 2000 of US$2 per dose for a three-dose schedule, Hib is significantly more expensive than traditional vaccines. In this sense, it is like the HepB vaccine. Perhaps more important for Hib, however, is the fact that many governments are simply not convinced that the disease is a problem in their country. Despite being a major cause of bacterial meningitis and pneumonia in young children worldwide, the Hib bacterium is difficult to isolate without invasive procedures – all pneumonia, the most common result of the Hib bacteria, looks alike so doctors and public health professionals rarely diagnose or think about Hib.

By the mid-1990s international efforts to increase children's access to Hib vaccines in the developing world began in earnest. These efforts, led by a number of scientific and public health champions, centred on establishing and communicating the burden of Hib disease. In the Gambia, West Africa, between 1993 and 1995, researchers assessed the impact of a Hib conjugate vaccine on the incidence of pneumonia overall in a double-blind trial involving over 40 000 infants, and concluded that one in five episodes of severe childhood pneumonia in the Gambia was Hib-related. Researchers in Chile have performed similar studies with very similar results. As a result, a handful of countries outside the established industrialized economies pioneered the introduction of Hib vaccine – mostly in Latin America and some in Africa.

In 1998 WHO published a position paper recommending use of Hib conjugate vaccines in routine infant immunization programmes. Two years later, a Hib vaccine trial similar to those in Latin America and Africa was undertaken in Lombok, Indonesia with the

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[1] See footnote 2, page 163 or Global Alliance for Vaccines and Immunization, 2001 for details.

[2] Global reported coverage in 2002 was 44 per cent (WHO-UNICEF estimate: 32 per cent). In WHO's Africa region, 25 per cent (6 per cent); Americas 74 per cent (58 per cent); South-East Asia 12 per cent (9 per cent). WHO, 2003.

[3] Until the late 1980s, the only available Hib vaccines were based on the polysaccharide, or sugary, capsule of the bacterium. These vaccines were protective in older children and adults, but not in infants – those at greatest risk of infection – because their immune systems could not respond. The new generation of conjugate vaccines contain two components: the Hib polysaccharide capsule and, attached to it, a carrier protein antigen such as tetanus toxoid which stimulates a strong T-cell related immune response from the infant immune system. Several Hib conjugate vaccines have been licensed, including combinations with DTP and DTP plus hepatitis B. For further details see P. Brown, forthcoming.

aim of increasing awareness and uptake in Asia. Uptake today remains low – the WHO estimates 9 per cent (12 per cent reported) in the South-East Asia region in 2002 (WHO, 2003).

In fact, based on the growing data on burden of disease and the still disappointingly low rates of uptake, GAVI has set itself a target of introducing the Hib vaccine to 50 per cent of high-burden, low-income countries by 2005. If they achieve this target, they will still reach only half of the people who need this vaccine most, more than 25 years after it was made available.

Current efforts

Preparing for a vaccine against meningitis A

Africa, in particular the 'meningitis belt' that stretches from the Gambia and Senegal in the west to Ethiopia and Somalia in the east, needs an effective vaccine against meningitis. The majority of meningitis cases in Africa are caused by the serogroup meningococcal A. The technology required to make a suitable vaccine is known, but no product has yet been developed.[1] In fact, vaccine manufacturers had begun to work on a vaccine in the 1990s, but discontinued these projects by the end of that decade. The low level of research and development in this vaccine has been attributed to "doubts about the ability to deliver the vaccine in some of the poorest countries with weak immunization infrastructure, the future prioritization of introducing meningococcal vaccines versus other disease efforts, and the future willingness to actually purchase a vaccine at a 'reasonable' price" (Batson et al, 2003).

The Meningitis Vaccine Project (MVP) was created by WHO and the Program for Appropriate Technology in Health (PATH) in 2001, with a US$70 million grant from the Bill & Melinda Gates Foundation, to accelerate the development of a group A meningococcal conjugate vaccine and ensure it is "widely used in 1- to 29-year olds to control [the] disease". The vaccine is also intended for use "as an EPI antigen in children under one year of age" (LaForce, 2003). Affordability is a core principle of the project, and MVP has committed to delivering a vaccine priced at "well under $1 per dose" (LaForce, 2003).

MVP defines four strategic areas of focus: vaccine development; research and surveillance; vaccine roll-out and distribution; and communications, advocacy and resource mobilization. It sees all four areas as "critically interlinked not sequential",[2] and as such has engaged in a unique demand creation and signalling mechanism to stimulate vaccine production and supply.

Early in its life, MVP concluded that multinational pharmaceutical companies would not be core suppliers of an affordable (< US$1 per dose) monovalent A conjugate vaccine. Instead, they focused on transferring conjugation technology from developed world collaborators to a developing world manufacturer that could scale-up, produce, lyophilize, pack, store and distribute the vaccine. As part of this effort to engage a sustainable supplier, MVP is currently negotiating an offtake agreement for the future vaccine in order to secure long-term supply at low and predictable transfer prices.

Simultaneously, MVP is preparing the groundwork for uptake by working with ministers of health and finance in Africa to build awareness and demand, and working with the donor community to secure financial support.

The final results of MVP's efforts remain to be seen, but progress is clear. Clinical lots of product are expected to be ready this year and phase I trials will begin in sites across the 'meningitis belt' in early 2005.[3]

Accelerated Development and Introduction Plans for pneumococcal and rotavirus vaccines

The Accelerated Development and Introduction Plans (ADIPs) currently in place for pneumococcal and rotavirus vaccines represent another concerted effort on the part of donors to reduce the time lag between introduction of products for industrialized and developing nations, and to speed breadth of coverage in the

[1] Polysaccharide vaccines were developed in response to epidemics of meningitis in industrialized countries in the 1960s. These vaccines are also used in developing countries but in response to periodic epidemics rather than in routine immunization; their effect in Africa is limited, both by immunogenicity and method of use. Conjugate vaccines are in general more effective, particularly in infants. In the 1990s, pharmaceutical companies were in the process of developing a conjugate A-C vaccine, but instead focused solely on a meningococcal C product when the UK government issued a request to purchase in 1999. A mening conjugate vaccine against serogroup C was developed for the UK soon after. For further details, see LaForce 2003 and the Meningitis Vaccine Project website (www.meningvax.org).

[2] From telephone interview with Marc LaForce, MVP.1

[3] Ibid.

developing world. The ADIPs are sponsored by GAVI with an initial investment of US$30 million, and are modelled after pre-launch teams that pave the way for the introduction of new commercial products. They are meant to be three-year projects that alleviate some of the demand uncertainty faced by manufacturers, and provide countries with the "information required to make the best choice about introduction".[1]

The ADIPs for both pneumococcal and rotavirus vaccines focus on three main sets of activities: establishing the value of the vaccine, communicating value and delivering value. Again, these are parallel – not sequential – activities.

The objective of 'establishing the value' is that burden of disease should be established and that the benefit of the vaccine be well understood at the country level. This requires disease burden studies, efficacy trials and other fact-gathering activities to prepare the case. Establishing value will also require a first assessment of latent demand, and an initial price estimate.

'Communicating value' is a unique recognition that education is a critical part of making the right decisions. The goal of these activities is to craft a message that convinces decision-makers to prioritize introduction of the vaccine where it is appropriate, e.g. through advocacy and demonstration trials, and commit to long-term use.

Finally, a reliable and sustainable supply of the vaccine as well as continued prioritization by national authorities will be required to 'deliver its value'. ADIPs will work to assure long-term supply and delivery with sustainable funding.

Both the pneumococcal and rotavirus ADIPs are seeking to identify 'early adopter' countries which will be the first to introduce their respective vaccines. These adopters will become the priority focus in terms of enhanced disease surveillance, demonstration projects and eventual introduction. Success in these countries will then lead to introduction and success in 'early majority' and 'late majority' countries. This user segmentation reflects the varied need, capacity and willingness of countries to adopt new vaccine technologies, and adapts commercial approaches to market segmentation and phased introduction.

In parallel, the ADIPs are working with multinational pharmaceutical companies – the suppliers closest to market for both pneumococcus and rotavirus vaccines for the developing world – to negotiate pricing arrangements. All of this is being done while products are still in development so the ADIPS are potentially shaping the products being created and explicitly trying to influence future supply dynamics.

Ensuring access to AIDS vaccines

The International AIDS Vaccine Alliance (IAVI) has already begun to consider the issues around access to AIDS vaccines for the poor, though the development of these vaccines is still in its early stages. A study commissioned by IAVI in 2000 (Widdus, 2000) recommended five essential steps to ensuring simultaneous worldwide access to AIDS vaccines as soon as they were ready for market:

1. Effective pricing and global financing mechanisms developed in advance, to ensure products could be promptly available for use where they are needed.
2. Mechanisms need to be developed to make reliable estimates of demand for specific vaccines and to ensure creation of production capacity to permit accelerated worldwide access.
3. Appropriate delivery systems, policies and procedures need to be developed for adolescents, sexually active adults and other at-risk populations.
4. National regulations and international guidelines governing vaccine approval and use must be harmonized.
5. Immediate efforts should be undertaken to achieve maximum use in developing countries of one or more currently underutilized non-AIDS vaccines in order to demonstrate global commitment to effective worldwide deployment of important vaccines.

A second study (Madrid, 2001) focused on specific actions that governments could take to facilitate the above goals, including support for regulatory reform and tiered pricing. This is an important reminder that PPPs may be the lead champions of these efforts, but success will require others to act as well.

In addition to further work to detail the above recommendations, two complementary need and demand estimation exercises are already well under way: a joint IAVI-WHO-UNAIDS project and a European Commission-funded World Bank project.

[1] From telephone interview with Orin Levine.

This integrated approach for an early-stage vaccine reflects a new and important shift in thinking about how best to prepare for the introduction and use of a new product in the developing world. In this forward thinking, the international community may have an unprecedented opportunity to influence the vaccine being developed, so that it is useful for (and compatible with) conditions in the developing world.

Guaranteeing a market through advance contracting

One way the donor community could enhance the market for new global health vaccines is by funding multi-year advance guarantee agreements. These commitments take the form of specific legal contracts to encourage the production of existing vaccines or the development of new vaccines, e.g. near-term vaccines like rotavirus and pneumococcus, or early-stage vaccines for HIV, TB and malaria. In either scenario, these contracts would be closely associated with estimated demand from developing countries and provide for some sort of price guarantee as a means of offsetting some of the risks facing vaccine manufacturers. In addition, these contracts may need to allow for 'dynamic pricing', i.e., allowing for higher prices when a product is first introduced (when quantities tend to be lower) and then reduced prices over time as volumes increase and, eventually, as developing countries assume the responsibility for payment. Liability and the overall credibility of the offer are two important issues that must be addressed for this mechanism to have impact.

The Pull Mechanisms Working Group – funded by the Bill & Melinda Gates Foundation and convened by the Global Health Policy Research Network at the Center for Global Development – has spent the past year evaluating the feasibility and potential impact of these tools in the PD portfolio, and has delivered preliminary conclusions that confirm both their practicality and importance.[1]

Emerging lessons

In order to meet their public health objectives in a particular disease area, PPPs must be concerned with mitigating both upstream and downstream risks in the vaccine market. Direct push funding will facilitate research and product development by directly reducing cost and therefore risk. But laying the groundwork for product introduction and sustained use – by creating predictable demand and securing financing – is essential to affecting both the timing and the speed of uptake, and the nature of supply itself.

Concern with the market requires more than the traditional approach of having sympathetic experts in Washington or Geneva understand the global burden of disease. Concern with the market requires demand creation in the developing world – by communicating the value of the vaccine to its users and understanding demand constraints like willingness and ability to pay. It requires demand signalling to reduce unpredictability for industry – by demonstrating willingness to purchase, guaranteeing willingness to pay or even generating a credible demand estimate. And it requires fund-raising and financial planning to support the market. New resources offered through institutions like GAVI and the Vaccine Fund create a unique opportunity to improve on a poor track record of vaccine introduction. The lessons of HepB and Hib have led to new approaches being implemented today. The results of these new initiatives have yet to be proven, but progress is promising. At a minimum the vaccine community appears to be converging around some critical success factors for new product introduction.

Start early

Planning for introduction when a product is on the market is already too late. Past experiences with hepatitis B and Hib demonstrate the dangers of such an approach: products were not produced in a profile or at a price that would serve the needs of the developing world; it took years to generate the demand, financing and international support to affect change in the product profile; and the work continues even today – more than 20 years after the introduction of the original product– to reach the full life-saving potential of these vaccines in the developing world. Preparing for uptake must run in parallel with product development. Starting early to create the market, e.g. through burden of disease assessment and communications with countries and with the donor community, is critical to accelerating the impact of vaccines once introduced. Equally important, however, is the opportunity to use demand

[1] Report of the Pull Mechanisms Working Group forthcoming from the Center for Global Development. Contact Ruth Levine (rlevine@cgdev.org) for details.

as leverage to shape the products being developed today. This is, after all, how PD works in industrialized markets – insight into what a market wants to buy drives innovation and product development. Advance demand planning gives the international community unprecedented leverage to partner with industry early in the PD process to ensure the most practical and useful vaccine is developed for those who need it most. This may fundamentally affect the product (e.g., a vaccine that targets African clades of HIV) or be a minor tweak that significantly affects usage in the field (e.g. testing a product's full thermostability instead of the standard 2–8 degree range). Finally, thinking early about financial sustainability and a long-term supplier landscape may have an impact on push funding or intellectual property decisions today.

Take an integrated approach

Preparing for uptake is more than just estimating need or even estimating demand, it is an integrated package of measurement, education, understanding and persuasion that must affect demand, supply and financing. If sustained use of a new product is the end goal, then all three of these pieces must be addressed together in an introduction strategy. Demand for most products, including vaccines, is created; willingness to use can and often must be created through education about the burden of disease and communication about the value of a vaccine; ability to use may require some parallel investment in health systems. Supply will clearly be shaped by the nature and value of demand – commercial entities will respond to credible demand estimates (both for quantity and also for product profile) as they invest in research, development, clinical trials, capacity installation and licensure. The international community must not only understand when and how it can affect these supply decisions, but also engage in an evidence-based dialogue with industry in order to lay the foundations for sustainable supply. Finally financing – the glue that will link supply and demand – must be in place in advance to leverage the power of demand today and ensure long-term supply into the future.

Commit to a long-term vision

Neither product development nor introduction is a goal in itself. It is the long-term vision of reducing burden of disease that motivates the key stakeholders, and therefore should be the starting point for all intermediate steps. PD and planning for introduction must be undertaken with a view to accelerating time to market maturity, and more importantly a particular vision of how that mature market will impact public health. The mature market will combine sustainable supply at affordable prices with sustainable use for all those countries that need and want the product – and this vision will have immediate impact in terms of target product profiles, demand forecasts, prices paid in the initial years, desired number of suppliers and the amount/structure of financing that must be in place today. It is, however, a long-term vision with many moving parts and therefore must be approached on a realistic time horizon. The phased introduction approach of the ADIPs may offer some lessons on setting intermediate goals in an integrated long-term planning process, for example, to get a product developed (years 0–5 for the near-term candidates of the current ADIPs), to introduce in early adopter countries (years 6–9), to spread broader coverage with multiple suppliers (years 10–13), and finally to reach market maturity (years 13–15). These stages then have implications for financing needs and priority PPP activities today.

Dedicate the capacity to do it right

Planning for product introduction requires supplementing existing public health and scientific expertise in PPPs with a particular skill set analogous to product launch teams in a pharmaceutical or biotechnology company. These teams may include scientists and portfolio managers, but should also include people with business development, market planning and marketing skills. The key activities required for successful uptake planning certainly include disease surveillance, but also demand estimation, marketing and communications, financial planning and knowledge of commercial product development practices. This is not a part-time job; it requires dedicated capacity to do it correctly and probably requires funding upfront to be most efficient. These skills are available for hire but should also be internalized in the international community so public sector 'product launch teams' can be assembled as needed.

If we get this right, there will be increasing numbers of products for which this type of upfront plan-

ning is critical to achieving meaningful health impact. This is a virtuous cycle that needs to begin today.

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In addition to the references cited below, this document was prepared following telephone interviews and e-mail exchanges with: Amie Batson, Senior Health Specialist, The World Bank; Alan Brooks, Senior Program Officer, Bill & Melinda Gates Children's Vaccine Program at PATH; Paul Fife, Health Advisor at the Center for Health and Social Development, Norway; Marc LaForce, Director of the MVP; Orin Levine, Director of GAVI's Pneumococcal ADIP; and Ruth Levine, Director of the Global Health Policy Research Network, Center for Global Development.

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ANNEX 9J

The costs of developing vaccines: Case study of VaxGen's HIV candidate vaccine

Donald P. Francis (Brisbane, CA, USA)

Executive summary

In recent years, great progress has been made towards both the understanding of infectious diseases and the means by which to make vaccines to prevent them. However, the powerful tools that have been developed to make vaccines can be used just as effectively to make other pharmaceutical products. Thus, there is competition for their use. Unfortunately, market forces, driven by social values and financial resources of the industrialized countries, direct these tools away from the development of important vaccines for developing countries towards that of high-profit therapeutic drugs for wealthier parts of the world. As a result, few urgently needed vaccines are being developed. Unless new models are constructed which alter this paradigm, the full power of modern science will not be harnessed to prevent disease in the less developed parts of the world.

Here, the example of the development of a candidate HIV vaccine is presented. This vaccine, know as AIDSVAX, required over 20 years of development time costing approximately US$200 million. AIDSVAX was evaluated in very high-quality studies in Thailand, demonstrating that world-class vaccine trials can be successfully completed in many areas of the world. With minimal efficacy measured in the phase III studies, development of this vaccine is far from complete.

In the end, the problem is not the lack of either the scientific/technical tools to make vaccines or our ability to conduct complex clinical vaccine trials in regions where tropical diseases exist. The problem rests with the will and commitment to finance the development of these important public health tools.

The cost of developing any new pharmaceutical product is high. A recent study from Tufts University (USA) estimated the cost required to develop a single drug to be US$802 million.[1] Although some have debated the exact number, no one will debate that it costs several hundred million dollars for each product brought to market. This is true for therapeutic drugs as well as preventive vaccines.

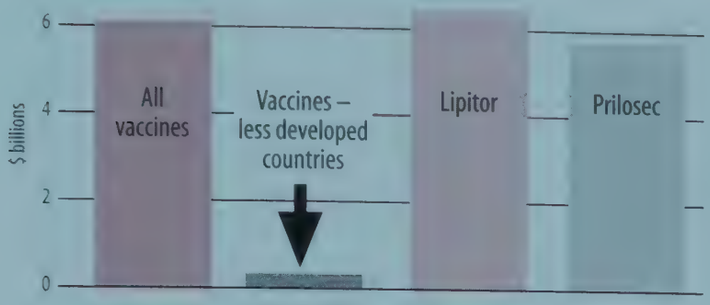
Despite the large costs, pharmaceutical companies continue to invest in drug development for the potential benefits (profits) received from successful products. For example, products like atorvastatin (Lipitor) and omeprazole (Prilosec) each bring in revenue of approximately US$6 billion per year. Evidently, society values these drugs that, respectively, lower cholesterol and decrease heartburn. These high-profit drugs are the 'blockbuster' products that all pharmaceutical companies seek.

Vaccines, unfortunately, do not fit into this 'blockbuster' category. The atorvastatin/omeprazole revenues far outstrip revenues from any vaccine. Indeed, the annual revenue for one of these drugs is equivalent to *all* vaccines combined! Moreover, the modest revenue from currently marketed vaccines comes primarily from selling products in industrialized countries. The minimal revenues from sales in the developing world hardly register on the same scale (*see* Figure 1). Thus, the financial incentive for pharmaceutical companies to develop vaccines for the developing world – extremely important products by anyone's assessment – is minimal.

In the field of AIDS, and as is the case for other infectious diseases, therapeutic drug candidates and vaccine candidates compete for the same development resources. Looking back, most would have anticipated that an HIV vaccine would have successfully completed

[1] Frank RG, J. *Health Economics* 2003; 22:325–330.

Figure 1. Annual revenue from 'blockbuster' drugs vs. vaccines

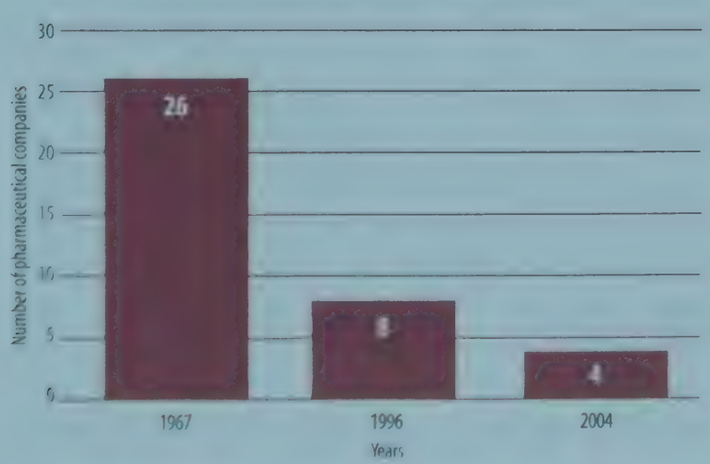


the development process far earlier than an HIV antiviral agent. At the time of the discovery of HIV, there were far more viral vaccines available than there were antiviral therapeutic drugs. But the opposite happened. Despite the immense challenge of developing antiviral drugs, more than a dozen are currently available for use whereas there is still no vaccine. I do not believe this reflects a contrast in the scientific difficulty to develop a vaccine versus a therapeutic. Instead, I believe it is the imbalance of market forces that has driven industry towards antiviral agents where the profits are far greater.

No one would debate that the social need for vaccines is enormous. But this immense need is not met with the financial resources to drive development of these products. Thus, although the social need is there, it does not translate into a social valuation high enough to drive industry to produce. Such 'market failures' of vaccines have received extensive discussions in the literature, including some dealing specifically with AIDS vaccines.[1]

With such an imbalance, it should come as no surprise that many large pharmaceutical companies have abandoned the vaccine business (*see* Figure 2). As a result, the number of vaccines being developed is small compared to the number of therapeutic products in the development pipeline. This is despite the monumental advances that have been made in microbial genetics, immunologic methods, recombinant DNA technology and manufacturing. With these new tools, the ability to make safe, effective and economical vaccines has vastly increased in recent years. Yet, the number of products in the pipeline does not approach the potential that modern science offers.

Figure 2. Large pharmaceutical companies developing and marketing vaccines, 1967–2004



One is tempted here to say that such a situation is the fault of the pharmaceutical industry. It is not. Society, in its wisdom, decides, directly or indirectly, what products it wants (values) and industry attempts to fill the resulting void. If society valued vaccines (i.e. would pay for them), industry would develop them to meet that value. Putting yourself in the position of a board member of a pharmaceutical company makes it easy to see why decisions are made not to develop vaccines. Board members have the legal responsibility to make decisions that maximize the financial return for their investors. If the choice before you, the board member, is to invest corporate resources into developing a potential blockbuster drug or a vaccine, the decision you will make is obvious – go for the blockbuster. Unless equivalent profits can be expected from vaccines, they will not be developed by industry. If each new drug or vaccine consumes the same development costs, why would you choose to invest in the low-yield vaccines over the high-yield therapeutic drugs?

All must recognize that the expertise to develop vaccines rests primarily within the pharmaceutical industry. Basic research often comes from university or government laboratories, but moving such discovery from the bench to a final vaccine product requires the expertise that rests in industry. If industry continues to abandon the vaccine field, fewer and fewer vaccines will be developed. Unless a new model is constructed where publicly supported institutes/projects, having industrial expertise, are funded to develop vaccines ('push'), or major funds are established to purchase vaccines ('pull'), little change will be forthcoming. This

[1] Batson A, Ainsworth M. Private investment in AIDS vaccine development: obstacles and solutions. *WHO Bulletin*, 2001, 79:721–726.

unfortunate situation is true for the industrialized parts of the world where limited potential profit keeps some vaccine development alive. For the less developed parts of the world, it is nearly hopeless with the current model.

Perhaps we can gain some insight into what is required to develop a vaccine by examining the AIDSVAX story.[1] It will also help the reader to better understand the considerable effort required to bring these products from the bench to the public. What is important in this review is to understand that the effort required to develop AIDSVAX is similar to the effort required to develop any pharmaceutical product. Thus, from a company's standpoint, a decision-maker must decide if the company is going to expend this effort on the development of a vaccine that has a questionable potential market or on a therapeutic drug whose potential market is much greater.

For HIV/AIDS, there is an obvious social need. The medical and social costs for AIDS have been substantial for almost all countries of the world. For sub-Saharan Africa, with upwards of 30% of the adult populations infected with this nearly 100% fatal virus, the adverse impact is stunning. Here the demand for a vaccine should be obvious. Indeed, from a social vantage point, the several hundred million dollar development costs for a vaccine are small compared to the tens of billion dollars in direct medical costs that HIV/AIDS accumulates each year.[2] One would think, given this immense economic, public health and personal threat, that dozens of HIV vaccines would have completed phase III by now and at least several would be licensed. But none has been. Unfortunately, the world is not always logical.

For VaxGen's vaccine, a total of 20 years has been consumed to date and development is far from complete. Genentech started the project in 1984 and stopped after the 1994 decision by the United States' National Institutes of Health (NIH) not to fund the phase III trial. VaxGen was then established to complete the development and, after receiving private funding, restarted the programme in 1997. Two candidate vaccines were developed – one matched to HIV subtypes found in North America and Europe and the other matched viruses found in South-East Asia. The phase I/I studies in the United States and Thailand were conducted between 1997 and 1999. The phase III studies, one in North America and Europe and one in Thailand, were completed in 2002 and 2003 (*see* Figure 3). Unfortunately, the vaccines' efficacy measured in these trials was low and much additional development will be required.

The expense for such an endeavour can be measured from at least two points of reference. One is direct financial cost. It is estimated that Genentech spent US$50 million in the early stages of development. In addition, VaxGen spent approximately US$130 million, the US government contributed another US$11 million (plus in-kind efforts by CDC in Thailand) and, in the final months of the Thai trial, the Bill and Melinda Gates Foundation contributed US$2 million (Table 1). Thus, in total, the vaccine development, manufacturing and clinical trials, including two large phase III trials, cost almost US$200 million.

Besides being time consuming and expensive, vaccine-development programsmes, like the one for AIDSVAX, are complex and require multiple, highly trained teams with skills ranging from laboratory testing and manufacture to clinical research and regulatory affairs. VaxGen employed over 100 people to conduct these trials. An additional 800 people were employed outside of VaxGen in four countries and 78 clinical sites. Over 12 000 volunteers were screened to identify the 7 930 volunteers for the two studies. These volunteers had over 135 000 clinic visits, 55 000 in-

Table 1. Approximate costs of AIDSVAX's development, 1984–2004

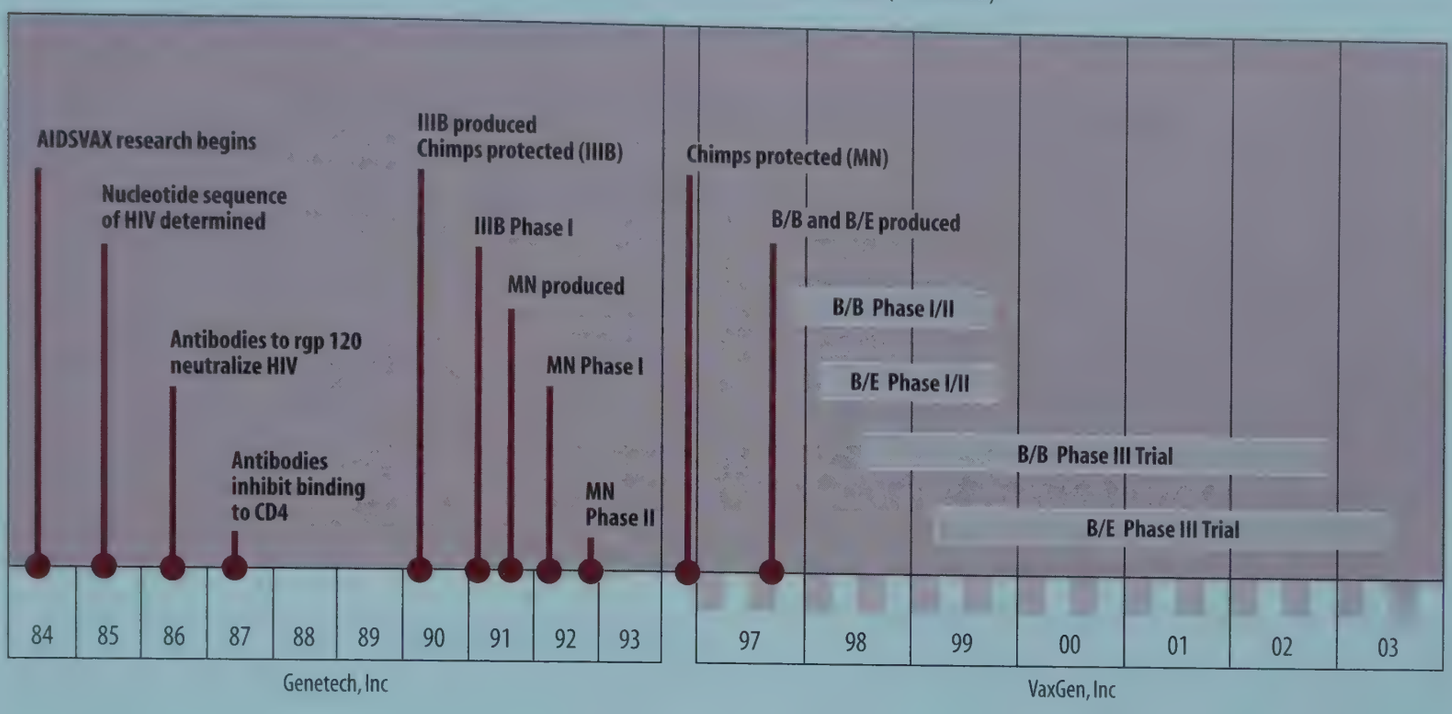
	US$ million
Genentech*	50
VaxGen*	130
US government +	11
Bill & Melinda Gates Foundation	2
Total	**193**

* Private investment
\+ CDC and NIH
(Does not include US$100 million for manufacturing facility in Republic of Korea.)

[1] Francis DP, Heyward WL, Popovic V, et al. Candidate HIV/AIDS vaccines: lessons learned from the world's first phase III efficacy trials. *AIDS* 2003, 17:147–156.

[2] Mann J, Tarantola D (eds) *AIDS in the World II*. Oxford: Oxford University Press, 1996.

Figure 3. Development timeline for candidate HIV vaccine, AIDSVAX
AIDSVAX B/B for North America and Europe; AIDSVAX B/E for East Asia (Thailand)



jections and 71 000 blood draws, and submitted over 1 million case-report forms. Each blood specimen had to be processed, stored and tested. Each case-report form had to be entered into a database. In the end, all of the data had to be analysed.

Important for this discussion was the success of the Thai investigators in conducting the world's first large, phase III trial of a candidate AIDS vaccine in the developing world. As mentioned above, such trials, especially given the Good Clinical Practice standards required by international regulatory authorities, are complex. Yet, investigators, regulatory and ethical oversight committees, and clinics dealing with volunteers planned and conducted the Thai trial to the highest standards. Thus, the experience in Thailand added further evidence supporting the feasibility of conducting challenging vaccine trials in less developed areas of the world.

Interestingly, the costs for the development and trials were not much different for the Thai or North American/European vaccine. The laboratory development costs and manufacturing for the two vaccines were identical. For the clinical trials, the most expensive part of vaccine development, the costs per –volunteer, were only slightly less in Thailand than in the United States, Canada and the Netherlands. The Thai trial enrolled 2 527 volunteers and the North American/European trial enrolled 5 403 volunteers. Paralleling the number of volunteers in each trial, the actual costs for the Thai trial were about half of the larger, North American/European counterpart.

A second point of reference involves the opportunity costs. The money and person years expended to do this effort are large and, if not invested in HIV/AIDS vaccines, could have been invested in something else with, perhaps, more chance of success. US$ 200 million is a considerable amount of cash. But cash can be replaced. Time cannot. Twenty years forms a substantial portion of a company's history and the careers of its staff.

In summary, there exists a huge potential health benefit offered by the recent immense advancements in modern science and vaccinology. Although small in relation to the costs of the targeted disease, the costs of moving bench-science advancements to new vaccines are considerable. Currently, no well developed system exists that either pushes or pulls vaccine developers to develop new vaccines against diseases that are prevalent in the less developed parts of the world.

In the end, it is social value. If society values vaccines for diseases like AIDS, and if that value is translated into well coordinated efforts to develop them, they will be developed. Viewed objectively, the problem is simple. It is us.

ANNEX 9K

Requirements for vaccine product and field site development at a licensure standard

Jerald C. Sadoff (Aeras Global TB Vaccine Foundation, USA)

Executive summary

Field site preparation, clinical testing, process development, manufacturing and licensing of a new vaccine in the developing world will cost at least US$150 million depending on the product and market requirements. Total costs for preparing two sites for phase III clinical trials providing the necessary infrastructure, epidemiology and phase I and II trials will be around US$14 million. Phase III clinical trials in 10 000 subjects carried out in these two sites including product cost will be around US$26.5 million. The process development will be US$12–15 million. A total of approximately US$55 million will be required to do everything necessary for a 10 000-subject efficacy trial running at licence standard. A US$100 million estimate for factory construction is on the low side and dependent on yield and market requirements.

An overall plan

Field sites and vaccine process and analytic development should be designed with the view to supporting the licence-granting procedure so that the vaccine can be used by millions of individuals in the developing world. This field site and vaccine product development (PD) is therefore part of a PD plan with milestones and 'go/no-go' decisions. In its initial iteration, this plan contains the pipeline of lead, back-up and second-generation products, a rudimentary product profile for these vaccines, product and assay development timelines and an early clinical development plan for the lead candidates. Eventually this plan becomes highly detailed and goes all the way through to full-scale manufacturing. This is a time- and resource-driven plan that incorporates known risks to shorten as much as possible the time taken to launch and make available the new vaccine. This balance between time, resources and risk is the critical part of the overall plan. The ability to convince talented local investigators to take ownership of the project and dedicate themselves to its design and execution will ultimately, however, determine its success.

Field site development

The best way to develop a field site is to actually perform a vaccine trial. This will provide the real basis for understanding the political, legal, infrastructural, logistic, communication, scientific and professional development and other requirements unique to the particular site. Obviously the best way to carry out a successful vaccine trial is to perform it in a site and with investigators where a successful vaccine licensing trial has recently been performed. If this is not possible, then in the two or three years of ramp up, phase I and II studies should be conducted at the field site and an epidemiological cohort study performed. This study should be designed with enrolment entry, informed consent, case report forms, case detection and follow-up, monitoring and data management systems similar to those to be used in the trial. The study will serve two functions: a logistic and professional development function and a scientific estimate of disease incidence and volunteer drop-out rates.

Certain fundamental things have to occur in order for a phase III vaccine study to lead successfully to the granting of a licence:

- First and foremost, the disease the vaccine is designed to protect against must occur in the immunized population at a rate consistent with predictions that the study sample sizes were based on. For this to occur, a well defined case definition is required at the time of epidemiological estimates as well as the curve of change of incidence of disease over time.

- Volunteer retention rates must be high because those lost to follow-up may be considered as vaccine failures in the intent-to-treat analysis, and thus eliminate the potential to demonstrate the vaccine's efficacy.
- Follow-up of all adverse events, especially serious adverse events and death, has to be very stringent. Verbal autopsies will not suffice; if that is all that can be obtained in the area the site may not be suitable for efficacy trials.
- Informed consent must be given properly. This requires considerable training of the personnel obtaining consent.
- Vaccine must be properly transported to and stored at the site, and administered.
- Blood samples must be properly drawn, processed, handled, transported and stored. Assays whose operational characteristics have been validated to an industry and regulatory standard must be used.
- Detection of disease must have an active surveillance component that is comprehensive and cannot rely entirely on a passive surveillance system. The sample size estimate and the disease incidence estimates must have taken into account the effect of this active surveillance and treatment. This requires assembly and training of active surveillance teams.
- The entire process of consent, immunization, adverse event follow-up, blood draws, follow-up visits, disease detection and all other aspects of protocol execution must be rigorously monitored at the site level and at the data safety and monitoring board (DSMB) level. Such monitors require training if not available and a rapid communication system between the field site and DSMB needs to be operational.
- All of the data collected in the study need to be put into a database. Reliable transport of the data to a common database is required. The data need to be checked for accuracy, consistency and completeness before the database can be locked prior to un-blinding. This has sometimes taken more than two years which is unacceptable. Current industry standards are 30 to 90 days.

A longitudinal cohort study utilizing the entry criteria, case definitions, consent forms, case report forms, active and passive surveillance systems, monitoring and data management systems, blood collection, processing and transport and assays envisioned for the phase III trial is the ideal way to ensure the professional development, logistical support, communications and infrastructure will be in place to support a well designed trial. Such a trial will also prepare community leaders as well as officials throughout the system for the phase III trial.

At the same time that the large longitudinal cohort study is under way, phase I and II vaccine trials in the population at the field site should also be undertaken. The local scientific community should be encouraged to become involved in the trials, so that they can benefit from early scientific papers on the vaccine. These trials will determine realistic time frames for ethical and regulatory review in the site and country. They will also flush out political and other problems that may be faced in the phase III trial.

A training programme to encourage professional development of those involved in implementing the trial is critical for success. The programme should include academic and practical aspects of GCP and other operational aspects of the trial and needs to be implemented early in the field site development plan.

The success of the phase I, II and III trials is totally dependent on identifying talented and dedicated local investigators who are integral to the design of all studies and their implementation. If it is a multi-centre trial, a local lead investigator should be in charge of the trial in the region and play a large role in the overall planning.

For generic costs, it takes about three years to develop capacity to do large clinical trials and that the total cost is approximately US $3.9 million, excluding the cost of phase I and II trials and the data management system. The costs would be more in the first year and less as time went on, but annual average costs are presented in Table 1.

Table 1

	US$
General infrastructure	100 000
Cohort studies	700 000
Laboratory capacity	300 000
Professional development	200 000
Total per year	1 300 000
Total (3 years)	3 900 000

This provides a community ready to enrol 4 000 to 5 000 people per year in a manner fully compliant with highest GCP standards. The cohort studies include a neonatal cohort and an adolescent cohort. The epidemiological parameters studied would be limited to baseline prevalence of infection and disease and annual risk of infection and disease and the requirements for cohort retention and formation would also be known. The laboratory capacity includes diagnostic labs and infrastructure to obtain, pre-process and transport immunology specimens.

The phase I studies cost around US$7 500/subject and the phase II around US$2 500/subject including monitoring. Data management would be around US$1 200/subject at this stage. For phase III study, costs are around US$1 500/subject plus US$1 000/subject for monitoring and data management. Laboratory costs of approximately US$1 million should be anticipated. Product costs of at least US$500 000 would be for consistency lots. Table 2 lists estimated costs for clinical phase I , II and III studies.

Table 2

	US$
Phase I (for 50 subjects):	435 000
Phase II (for 600 subjects):	2 220 000
Development of a validated assay:	500 000
Capacity Building (see Table 1)	3,900,000
Total cost over 3 years:	7 055 000
Phase III (10 000 subjects):	
Study costs:	15 000 000
Monitoring and data management:	10 000 000
Laboratory:	1 000 000
Product costs:	500 000
Total (for 10 000 subjects):	**26 500 000**

It is important to include the costs of phases I and II into the field trial development costs because a site cannot really be developed without performing these studies at the site. If more than one site is being contemplated, then the phase II studies can be divided between the sites.

Product development

Development of the processes for vaccine production and analytic tools for release and stability at licence standard should happen while field site development is occurring. Phase III trials should not begin with vaccines that are made by processes considerably different from those envisioned for full-scale manufacturing. Otherwise, despite the potential for bridging studies, the efficacy trials may need to be repeated. There is considerable controversy here, but it is generally accepted that a phase III efficacy trial should be performed with the final factory product or at least with a process that with some modifications can become a full-scale process.

The fundamental requirements that should be developed in order to make decisions concerning when to build and how to size factories are listed below. These critical decisions on when and how much capital to invest determines the timing of availability of vaccine. Lack of availability of certain vaccines for the developing world despite proven clinical efficacy has been a major tragedy in the past and continues today. The better the quality of the information about each of the five areas listed in Table 3, the sooner a vaccine can be made available and the more likely that investment will occur and will not be wasted.

Product profile characteristics of importance to manufacturing listed above, tied to product profile characteristics related to clinical performance of the vaccine such as efficacy, adverse event profile, delivery mechanism (i.e. needle, nose, oral) and costs, all affect estimates on the amount of vaccine needed for each territory as well as estimates on time to regulatory approval. These estimates, which justify the amount and timing of capital investment for factory construction, are therefore critical factors for success of public private partnerships attempting to save as many lives as possible.

Of course all costs are product related. Estimates derived from live viral vaccines and recombinant protein vaccines expressed in E. coli are listed in Table 4.

Table 3

1) A product profile in terms of:
   a. technical specifications for release of the product
   b. dosage
   c. regimen
   d. method of delivery
   e. target population
   f. final package
   g. multiple and single dose requirements
   h. Stability, storage and transport issues:
      i. minimum acceptable expiry period after shipping from factory
      ii. estimate of bulk and finished product storage requirements
      iii. Manufacturing window filling model which incorporates
         1. maximum potency at release in terms of clinical safety
         2. minimum potency at expiry in terms of clinical efficacy
      iv. Bulk stability data
      v. Final product stability data
      vi. Stability data during and following reconstitution out of storage
      vii. Stability data in relation to temperature and transport
   i. Estimates of costs of vaccine bulk, final product and packaged product.
2) A fully developed, reproducible and scaleable vaccine manufacturing process for transfer to a full scale manufacturing facility has been developed where:
   a. Estimates of yield at scale initially and after improvements are reasonably accurate
   b. Losses during downstream processing and lyophilization have been determined to satisfy overall yield estimates
   c. Processes are robust enough to reduce failure rates to an acceptable and predictable level
   d. Initial materials are readily available from reliable suppliers ideally with multiple sources
3) Fully developed, validated and statistically characterized release and stability assays which demonstrate:
   a. potency, based on well characterized and properly stored and characterized standards
   b. product purity
   c. freedom from adventitious agents
4) Roll-out of regulatory approvals in each territory including packag0 ing, pricing and other required governmental approvals.
5) Roll-out of estimated product requirements by quarter and territory following regulatory approval and other governmental approvals.

Table 4. Material for Phase II and potentially for Phase III

	US$
Process development	2–5 million
Vaccine	1 million
Final factory scale	
Process development	12–15 million
Factory design and construction	70–500 million
3 vaccine consistency lots (can possibly be sold)	100 000–1 500 000

ANNEX 9L

Product development public-private partnerships for diseases of poverty

Are there more efficient alternatives? Are there limitations?

Robert G. Ridley (Director, UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases)

Executive summary

A brief analysis of the alternatives to public private partnerships (PPPs) for product research and development (R&D) for diseases of poverty is presented. At their extremes these alternatives consist of private sector-driven and -managed R&D and public sector-driven and -managed R&D. It is concluded that the private sector alone will not collectively/competitively fully finance and manage product R&D unless the public sector injects many billions of dollars into creating a competitive market for such products. Similarly, the public sector cannot endeavour alone to take on the full role of innovators and providers of new products unless it is prepared to invest much more heavily, not just in financing R&D, but also in the sustainable generation of a capital-intensive product R&D infrastructure. Such an infrastructure, which currently resides in the private industrial sector, is necessary to provide any chance of sustained success in what is generally recognized to be a high-risk endeavour. It is concluded that PPPs, despite the cross-cultural challenges of managing activities across the public and private sectors, offer many advantages over product R&D undertaken solely by either the private sector or the public sector. This is especially the case when they are managed virtually with little need for additional capital investment. Furthermore there is limited evidence that the products generated through PPPs are efficiently generated and highly relevant to public health needs. Thus, PPPs should be further promoted and supported.

The current environment and landscape in which product R&D PPPs operate is assessed. It is noted that there has been a significant increase in product R&D activity but that this has been diverse and multi-organizational in nature. The total product R&D activity for diseases of poverty currently ranks at the level of a small pharmaceutical company, but there is a likely to be a doubling of size in the coming five years resulting in many more individuals being engaged in product R&D for diseases of poverty. There are several areas that warrant future discussion, support and oversight to ensure:

- The partnerships are neither over-competitive with each other, nor monopolistic
- There is a sense of common purpose and direction, and cross-linkages and synergies are facilitated
- The product profiles being sought by PPPs are in line with global health needs
- Exploratory research and early product R&D – translational research – is supported to ensure that pipelines are maintained
- Appropriate mechanisms are in place to ensure the continued and sustainable production of useful new products once they reach the market
- There is appropriate downstream research – transitional and implementation research – undertaken to optimize the use of the products and provide evidence for policy and implementation
- Conflicts of interest are minimized
- Capacity building and capacity utilization in developing countries is integrated into product R&D activities
- There should be strong stakeholdership from developing countries within the context of product R&D, product use and product delivery.

Product development public private partnerships for diseases of poverty. Are there more efficient alternatives? Are there limitations?

Introduction

The last several years has seen an explosion of product R&D-based not-for-profit organizations dedicated to develop new drugs, vaccines and diagnostics for diseases of poverty. Many of these classify themselves as public private partnerships, though some engage more readily with the private sector than others. Examples include: IAVI for HIV vaccines; MMV for malaria drugs; MVI and EMVI for malaria vaccines; GATB for TB drugs; Aeras for TB vaccines; IOWH for multiple diseases of poverty; DNDi also for multiple diseases of poverty; Microbicides Initiative; FIND for TB diagnostics, with possible expansion beyond TB. The vast majority of these organizations owe their existence to funding from a limited number of foundations and government donors. By far the largest of these is the Bill & Melinda Gates Foundation, though the Rockefeller Foundation has also been instrumental in many partnerships. In addition a variety of single PPP activities have been initiated such as the development of a diamidine for African trypanosomiasis, funded by the Gates Foundation, or the development of Lapdap for malaria, funded by the UK's DFID. For the purposes of this article, I may sometimes include foundations such as the Gates Foundation within the 'public sector', in that they are not-for-profit and are providing resources solely for the public good.

The PPP organizations have added to several public sector and philanthropy-based organizations and programmes that have long been active in this field and also partner with industry to deliver new products. Such organizations include WHO/TDR (Tropical Disease Research); WHO/HRP (Human Reproductive Programme); PATH (Program for Appropriate technology in Health), WRAIR (Walter Read Army Institute for Research), NIH Small Business Research Grants; and other national ad hoc programmes and projects. Special mention should be reserved here for the Chinese government-sponsored discovery and development of the artemisinin derivatives. These organizations have also added to the activities of several pharmaceutical companies that have been active in this field over the years, such as Merck, Roche, Aventis, GSK and Novartis, as well as numerous smaller companies. It is worth noting in passing that many additional companies also have programmes related to improving access to specific products, ranging from vitamin A to antiretrovirals (ARVs). In connection with product R&D the establishment of multimillion dollar drug discovery facilities by GSK (Madrid, malaria and TB), AstraZeneca (Bangalore, TB) and Novartis (Singapore, TB and dengue) should also be highlighted, as well as other industry initiatives such as Sanofi's malaria drug R&D programme.

With this background in mind, this paper will address two key issues:

- First, what are the alternatives to PPP? Are we correct to move down the PPP road? Should we instead, as some people have argued, focus on providing financial and market ('pull') incentives for industry to engage competitively in product R&D? Should we focus on developing public sector capacity to discover and develop, and hence own, products and thus bypass pharmaceutical companies altogether?
- Second, are there limitations, or gaps, in the landscape of the multiple organizations working to develop new products? If so, what are they and how can they be addressed?

Assessment of alternative options to, and unique characteristics of, PPPs

For the purposes of this discussion I will define a public private partnership as a project, or portfolio of projects, in which public or philanthropic funds and resources are combined with pharmaceutical company resources, in a functional partnership that is co-managed by both parties under an agreement that stipulates the terms of that arrangement and defines the product that is to be discovered/developed to meet a public health need.

By definition, this does not include products for which pharmaceutical companies identify a market opportunity, or a strategic objective, that justifies independent competitive activity. Currently antibiotics and antiretrovirals for HIV/AIDS fall into this non-PPP category.

The two extreme alternatives to PPP are: private sector-financed and -controlled product R&D and public sector-financed and -controlled product R&D. I will deal with each of these in turn and finally assess the attributes of product R&D PPPs before stating my conclusion.

Private sector R&D

I can classify two types of case where private sector-owned R&D could operate for diseases of poverty:

- First, if a company recognizes a commercial and/or strategic and/or philanthropic motive in developing a product by itself. Past examples of this include the development of coartem for malaria by Novartis and previous cases of antimalarial drug development during the 1980s and 1990s. It also applies to many diagnostics, of which I will say more below.
- Second, if a system (perhaps legislative) is put in place that offers sufficient (financial) incentive for companies to invest by themselves in developing and producing new products for specific indications. Examples of this are not yet found in the area of diseases of poverty, but can be found in the market exclusivity granted through orphan drug legislation for rare diseases of the North and in US legislation to promote the development of paediatric formulations. One might also classify the concept of the Global Fund for AIDS, TB and malaria as a potential non-legislative financial pull mechanism if the funds were adequate in size. At the moment they are self-evidently insufficient to have such an impact.

Taking the first case, history has shown that even if a few companies do take on the praiseworthy task of developing such products for limited financial gain, or for strategic/philanthropic reasons, the collective output does not result in a sustainable pipeline of innovative new products, especially in the case of drugs and vaccines. Excluding HIV/AIDS, the closest example we have over the past 50 years of industry working independently in this manner is for malaria, and that has obviously left us with an inadequate situation. I would also go further and add that the antimalarial products historically produced by such pharmaceutical companies have not always been primarily directed at the poorest of the poor, or even if they have, the lack of public sector/academic engagement in their development may have contributed to some of the limitations of those products.

Thus, malarone was developed for malaria primarily as a prophylactic agent. This is not to belittle the accomplishment or the medical need for this product, but it shows that not all products for the target diseases are automatically going to be of use to poor populations suffering from the disease. In the case of Coartem, the product is good, but its development – through the private sector route only – perhaps contributed to its slow introduction into widespread use. In addition, certain initial limitations on its label and use probably would have been averted if there had been stronger earlier public sector engagement. Coartem introduction was slow as the company needed, after marketing approval, to discuss with the public sector (in this case WHO), on the need, cost and other aspects of its introduction. In addition, due to its (label) use as either a 4-dose or 6-dose treatment and its limitation to children above 10 kg, further PPP research with TDR has had to be carried out to validate a 6-dose regimen in Africa and to demonstrate safety and efficacy in children down to 5 kg. This information is now about to be submitted to the Swiss regulatory agency.

No product, including one developed in PPP, should automatically find its way into public sector use. This can only occur if it demonstrates 'in real life' its superiority and value over other products and, in the case of drugs, justifies inclusion on national essential drugs lists. However, if a PPP-developed product has the relevant qualities, it often has the potential to be more readily transitioned into use. For example, the recently marketed products of Lapdap (GSK – TDR) for malaria and miltefosine (Zentaris – TDR) for visceral leishmaniasis are now already undergoing extensive post-regulatory investigation to provide evidence to inform policy-makers on their appropriate use.

For vaccines, where the technical hurdles are much greater than for drugs and diagnostics, the economic situation relating to private sector engagement for diseases of poverty is similar to that of drugs. In many cases we have been fortunate that advances in vaccine technology directed at the North has had benefits for the South (e.g., *Hemophilus Influenzae* type B vaccine, hepatitis vaccines, multi-component childhood vaccines). However, there are cases of vaccines being developed for diseases that had potential for use in the developing world, but for economic reasons, they have not been developed for such use within the private sector. A good example of this is meningitis. The meningitis belt across sub-Saharan Africa is not covered by the standard vaccine of the North because it results

from a different strain of meningococcus. A special PPP initiated by WHO, funded by the Gates Foundation and involving several other partners is now moving this development forward.

In the case of diagnostics, companies have invested in products for diseases of poverty, but due to small market size, small diagnostics companies predominate. In addition, due to a lack of regulatory oversight, a vast array of products may exist with little advice being available to the consumer, or purchasing organization, on their relative value. Once again, public sector engagement with companies after product approval is often necessary to enable the pubic sector to assess which products meet approved standards for public sector procurement. Examples of this approach have recently been undertaken by TDR in collaboration with WHO's Western Pacific Regional Office to establish criteria for the identification of malarial diagnostics that justify public sector procurement. Similar studies are being completed to establish which of the marketed syphilis diagnostics justify public sector procurement. It is noteworthy that so far in similar studies, none of the gonorrhoea or chlamydia diagnostics tests have been declared valid for public sector procurement. There are now some PPP projects being initiated where diagnostic products are developed in partnership from an early stage. For example, the development of a patch test diagnostic for onchocerciasis by TDR in collaboration with a German company, where extensive preclinical and clinical testing will provide evidence of value, prior to marketing and a decision by control programmes on its utilization. Other tests, including some for TB with TDR and FIND, are at late stages of development and once again extensive evidence will be generated to inform the public sector in advance of marketing on whether or not they justify procurement.

A final word needs to be made on biotech engagement in product R&D on drugs and vaccines for diseases of poverty. Biotech companies are indeed engines of innovation and due to their small size they can move very rapidly in areas in which they are specialized. This has led many to believe that biotechs are an answer to our problem if only we can appropriately employ diligent use of venture capital for investment. Evidence to date has not borne out this simplistic scenario, with several small 'profit venture capital'-driven initiatives failing to take off. There are two main reasons for this. Firstly, small biotech companies, even more acutely than large companies, have to cover their costs, especially if they are publicly listed and owned. Secondly, their future, just like that of large companies, is dependent upon making people believe that they have one or two products that will earn a significant financial return. Although they can write off some R&D costs by 'demonstrating' that their technology can produce a particular result or product in the 'diseases of poverty area', and thus gain credibility and further investment, ultimately such an investment is always a poor second to their core business. Although there are plenty of examples where biotech companies have 'tested the water' of neglected disease product R&D through limited initial investment, there are few if any cases where they have successfully continued to go ahead on their own, without significant public sector support. In the case of a few companies which have attempted this, that I am aware of, the companies are no longer in business.

The second case referred to at the beginning of this section relates to proposals that might entice the private sector to fully commit to product R&D for neglected diseases through the creation of financial incentives, including through legislation. There are no cases to date where this has been successfully achieved for diseases of poverty. The bottom line is that market sales for a product of at least US$200 million a year are needed to justify a company investing by itself in a portfolio of drug R&D projects. If multiple products are already on the market for a given indication, creating an element of competition, this makes the likelihood of reaching such sales figures even less. In addition if several of those products are, or will in the future become, generic, this puts further pressure on prices and profitability. One might in such cases require a total market size approaching US$1 billion to generate competitive industrial R&D. Furthermore, due to the political nature of the diseases in question, there is intense pressure on companies to keep their prices low once a product comes onto the market, further limiting profitability and incentive for investment.

Many ideas have been put forward to mitigate this situation, such as orphan drug legislation providing enhanced market exclusivity; tax breaks for both R&D and for provision of final product; and transferable credits for extending patent life and/or market exclusivity

on other profitable products. However, all of these require intense lobbying for legislative intervention, which may differ from country to country. Once one looks into the details of these proposals they become increasingly complex and potentially difficult to manage.

The idea of a grand prize for the development of an innovative tool such as a vaccine that meets pre-defined specifications has also been proposed. This seems simplistically straightforward. However, once again when one looks at the detail, problems arise. For example, what if a second, superior, product is developed soon after the first? Which product is put into use? Who gets the prize? Is some sort of sharing undertaken that devalues the reward? These are interesting questions but of course the whole idea is currently hypothetical because nobody has yet put up the money to back the idea.

I believe the bottom line is that companies will only be incentivized to engage competitively in product R&D if they see, and hence believe, that the public sector is investing funds in the purchase of existing tools. If they see the billions of dollars going into the purchase of tools that public health needs demand and that there is substance behind the rhetoric of providing increased resources, then they will invest. However, given that it takes many years to develop a drug or a vaccine they will also have to be convinced that public sector purchase will be sustained over the long term. It is also likely that companies will be very focused in their response. A huge increase in funds for antiretrovirals will only elicit a response for ARVs, not for other diseases of poverty.

Even the large funds moving into public sector purchase of ARVs, TB and malaria have not generated any sign of increased competitive private sector R&D. The increase in funds has, however, stimulated further competition and increased 'less risky' private sector investment in production and manufacture and improved formulations in these diseases, particularly in the generics sector. This suggests that if sufficient funds were provided to generate a strong market then independent private sector R&D could be stimulated.

In conclusion, many additional companies have become engaged in product R&D over the past five years. My belief is that this is only minimally due to increased public sector purchasing power, or the belief that there will in the future be such an increase. This expansion is mainly due to increased funds and resources available through product R&D PPPs to 'push' R&D, coupled with an increased political awareness by companies of the need to demonstrate good corporate citizenship.

Public sector R&D

It is stated by some individuals and organizations that there should be no reliance on the private sector for the generation of products and that the public sector should take a stronger lead and fully resource product R&D. In such cases it is often left open how the production, manufacture, distribution (and sale?) of these products should be managed.

There are several issues that need to be assessed in addressing this argument, over and above the philosophical/political arguments of the relative merits of the case. Philosophical and political positions equally impact on both free market proponents, as well as anti-free market proponents, who oppose PPPs. As there is often little that can be said to affect these opinions, no further discussion of this issue is warranted in this article.

With this philosophical/political caveat I would state the issues surrounding public sector driven product R&D are as follows: can public sector-dominated approaches produce tools of the quality and standards that we need? Can public sector-dominated approaches produce tools in a time-efficient and cost-effective manner?

There are case histories demonstrating that public sector-managed programmes can deliver new tools that justify clinical use. Perhaps the best historical example is the case of the early vaccine industry, which was built largely on public sector research leading to institutes, owned by the public sector, producing and manufacturing vaccines. However, it is notable that over recent years, this approach has become unsustainable, and the need for private investment to improve on existing technologies has resulted in R&D-based vaccine activities moving largely into the private sector. The other example that springs to mind is the R&D, production and manufacture of agents related to war and national security. Thus antidotes and vaccines against biological and chemical warfare agents are often developed and manufactured within the infrastructure of the public sector.

So, public sector R&D, manufacture and production are certainly achievable. However, globally, the

experience is that private sector-managed innovation has resulted in more, higher quality products. Most areas involving product R&D have therefore moved into the private sector. This has resulted in an extremely limited public sector infrastructure available to support product R&D. Where such infrastructure exists, it is also less likely to be as modern and up to date as in the private sector.

This lack of infrastructure and manpower in the public sector is highly significant. Any long term strategic public/philanthropic sector approach would require the provision of this infrastructure, which would require substantial and extensive capital investment. In order to recruit the necessary high-quality human expertise, there would be a need to offer incentives for scientists and technicians on a par with the private sector, further increasing costs. Furthermore, the availability of expertise that projects could draw upon would likely be significantly less in the public sector than in the private sector. The choice of people, of projects and of location where research could be undertaken, would all be substantially reduced.

In conclusion, a public sector-driven approach is 'doable', but would be extremely costly and capital intensive, due to the need to generate and sustain an extremely complex infrastructure. It would also result in less choice and reduced access to available expertise. Finally, there is always the added concern that if such a capital-intensive organization were placed entirely within the public sector, where there is also limited experience of governing such institutions, additional restrictions would inhibit progress.

Public Private R&D

Much has been written about PPPs and there is no need to repeat the concept in detail in this paper. However, I would draw out the main argumentation as to their added value over private or public sector programmes and present some limitations.

The claimed added value of such partnerships comes from:

- the utilization of both private sector expertise in product R&D and product specification, and public sector expertise in the diseases, populations of interest and the environments in which the products will have to be tested and ultimately used
- the sharing of resources for an activity thus limiting the risk to partners in both the private and the public sectors
- the sharing of existing infrastructure, limiting the need for capital outlay
- the use and combination of best practices of management, selection and review of projects from both sectors, and to secure avoidance of conflict of interest
- the potential ease of transition of new products into public sector use, based on a more detailed understanding by the public sector of the relevant merits and faults of any given product.

The potential negative elements of public private partnership include:

- the need to develop and operate a partnership under legal agreements that may involve different operational cultures
- complex virtual managerial structures for individual projects.

My belief is that the positive elements outweigh the negative, though it needs to be recognized that PPPs are not a panacea. In some cases mistakes will be made and projects and organizations will fail, not just due to science but also to inherent organizational and partnership reasons.

In summary, my personal conclusion is that unless the public sector is prepared to invest far more funds (many billions of dollars), either to ensure sufficient commercial 'pull' to get the private sector to invest competitively in R&D or to ensure that there is a viable capital intensive infrastructure for public sector R&D, then PPPs remain the only viable alternative for the foreseeable future. I would go further and state that even if the options were available to go down either the private sector or the public sector route, on balance PPPs have the capacity to deliver better products more suited to public health needs and to produce and get them into use more cost-effectively.

Assessment of the current operating environment of PPPs

The expansion of organizations engaging in PPPs has had the net effect of bringing in more public sector and philanthropic resources into product R&D for diseases of poverty. In the next paragraphs I will be referring to some financial estimates. I should stress that

these figures have not been closely researched, but represent 'ballpark' estimates based on my current understanding of what is happening in product R&D PPPs and in related activities. They need to be further researched and validated. However, I believe that they are useful in transmitting to you an idea of the scale of investment that we are talking about.

Back-of-envelope calculations suggest that focused product R&D funding from traditional organizations such as TDR, HRP, PATH, NIH, USAID, WRAIR, Wellcome Trust, EU and others, including various nationally supported projects, probably stands at around US$50 million. The increased expenditure due to new organizations probably adds around US$100 million per year, with potential to grow to around US$200 million a year over the next five years as these organizations further scale up. This does not count a lot of 'overhead' input from the public sector in terms of the university and organizational infrastructure that is also committed to these activities. It is difficult to calculate the in-kind commitment obtained from the private sector in partnership projects. However, it is likely that PPP institutional funding has leveraged at least an equivalent amount of resources from the private sector through the contribution of in-kind resources into projects. This is particularly the case if one counts investment in production and manufacturing. At an extreme, in the case of TDR's partnership with Zentaris to develop miltefosine, we have calculated that the ratio of company to public sector investment was greater than 10 to 1. If one takes into account the specific industry initiatives of GSK, AstraZeneca, Novartis and Sanofi, mentioned in the introduction, then the collective total will probably easily match that of the public sector. Thus we are talking of a total increase in resources of around US$200 million per year since the late 1990s, with the amount possibly rising to around US$400 million in the coming five years if current trends continue. By 2010 we might be talking of total product R&D levels for diseases of poverty, excluding HIV/AIDS drug R&D, of around US$500 million.

It is critically important to realize that these funds represent the input of additional personnel, people whose intellect, expertise and dedication would not be channelled into these endeavours unless these funds were available. If one assumes an average full-time equivalent (FTE) cost of around US$100,000 (this is a conservatively high 'guesstimate' based on the fact that it includes the high FTE costs of industry and well-paid public sector individuals, combined with the lower costs of scientists, technologists, post-doctoral fellows, graduates and technicians performing much of the work, and the increasing numbers of people engaged in developing countries, where personnel costs are low), then we are talking of the equivalent of 5 000 or more additional FTEs of people working on product R&D for neglected diseases by 2010.

As stated at the beginning of this section, these figures are extremely approximate and need further verification, but they give some idea of the scale and magnitude that we are discussing. To put this further into perspective, R&D expenditure of US$500 million is about 10 per cent of that found in the largest pharmaceutical companies and 5 000 people equates to about 25 per cent of R&D personnel found in large pharmaceutical companies.

This represents a significant body of activity, but it is characterized by its diversity and its multiplicity of activity. Whereas output from a single pharmaceutical company is coordinated and directed, the activity described above for PPP's comprises many individual partnerships each with their own goals, sometimes as part of a broader portfolio of activities and sometimes not. This multiplicity of activity brings to it an element of confusion amongst the donor community, those involved in health policy, governments of countries in which the products are to be utilized and the general public. This confusion can be further exacerbated as the general public and many of those overseeing the financing of health research in general often find it difficult to distinguish clearly between product R&D and research in general, and often even between drugs and vaccines.

I list below several areas where I feel specific attention needs to be paid as we move forward with expanding product R&D PPPs and providing the institutional and governance background support to ensure their success.

Partnerships should be neither over-competitive with each other nor monopolistic

There is increasing competition for funds to finance PPPs and other forms of health research. This is healthy,

especially if it results in a net increase of funds coming into the area. However, given the relatively small level of investment going into product R&D for diseases of poverty, we also need to have an environment of mutual support and interaction between organizations. There has been an explosion of improved and more professional 'advocacy and communication' activities, which again has been helpful in promoting the entire area. However, we have to be careful as a community that we distinguish between 'delivery' and 'promise' and between 'reality' and 'soundbite'. There is a need to avoid too much duplication of effort and, in the future, we may even be merging small organizations into larger ones. However, there is a need to ensure that no one organization creates an absolute monopoly in a given area. In any sphere of life, to put all ones hopes in one single organization can result in disappointment. The nature of innovation demands that there be a multiplicity of routes by which promising science can be converted into new tools and that no one person, organization or committee has complete global responsibility for one particular area.

A sense of common purpose and direction is needed that facilitates cross-linkages and synergies where appropriate

As mentioned above, the product R&D activities we are discussing represent a relatively small collective effort compared to the pharmaceutical industry. Just as for a pharmaceutical company, we need to focus on and generate new products. However, as a community interested in product R&D for diseases of poverty we are very diverse when compared to the cohesion of a single company. Recognizing that there are many players in R&D, that there are many stakeholders in the basic science from which product R&D is derived, and that many more stakeholders are involved in the end use of the products, there is a need to generate a common purpose and direction in this field. A common vision. This does not mean that there should be micromanagement of organisations, but that there should be discussion and consensus around the key elements of the types of product that we need (product profiles) and an understanding of the environments and health-care systems in which they will be used. Such 'common purpose' then makes it easier to link between organizations and generate synergies.

The product profiles being sought by PPPs should be in line with global health need

It is absolutely critical that the profiles of the products being sought are in line with medical needs and the limitations imposed on their use by human nature and social environments, i.e. that the products we produce are relevant for the populations for whom they are intended. This sounds straightforward, but it is a factor that can often be lost within the complex technical environment in which the products are generated, and where there is often a temptation to 'go early with what we have got', rather than to wait a little and 'go later with an optimal product'. In the past, with minimal R&D investment, we in the public sector have had to take the former philosophy. With increased resources we can now afford the luxury of moving toward the second philosophy. Once again, as intimated above, there is immense value in generating a broad consensus on product profiles and it is an area that justifies further discussion. By generating and publicizing such consensus we can ensure that multiple organizations are essentially 'pulling in the same direction'.

Exploratory research, and early product R&D – translational research – needs to be supported to ensure that product R&D pipelines are maintained

The focus on product R&D should not detract from the need to invest in the early stage research that is necessary to ensure a full pipeline of activities and so enhance the chances of success in delivering new products. Particularly important is the need to focus more investment in the area of 'translational research', research that moves an interesting scientific observation to a stage where it justifies significant investment to optimize it and develop it into a product for testing and clinical evaluation. In the area of drug discovery this requires the conversion of genomic information into robust biochemical assays and the availability of high throughput screening and other secondary activities to generate lead molecules worthy of optimization. For vaccines it may be that a particular promising antigen requires further optimization, scale-up of manufacture and detailed animal testing and process development. For diagnostics it may be that an early stage assay needs to be further optimized prior to its development into a format that is robust, quality assured and ready for evaluation.

Appropriate mechanisms need to be in place to ensure the continued and sustainable production and distribution of useful new products

In addition to the lack of engagement by major pharmaceutical companies in product R&D for diseases of poverty, there is a danger that a similar lack of engagement occurs in the production, manufacturing, marketing and distribution of products. As we move forward with an expanded agenda, this is particularly of concern for diagnostics and for drugs and other products for the smaller diseases. If a major R&D based company or a major generic company is the private sector partner then they can utilize their vast networks of affiliates to ensure marketing and distribution. If smaller companies are involved this might limit distribution and availability. Some interesting and innovative examples exist which show how such issues can be addressed. For example, the creation of a special not-for-profit organization, the Concept Foundation, was initiated to handle intellectual property rights and licensing issues associated with a new contraceptive developed through WHO's HRP. This initiative, created with support from the Rockefeller Foundation, has been highly successful in engaging with local manufacturers and distributors to ensure widespread availability of an affordable product. Even with the engagement of major pharmaceutical companies, there is an urgent need for complementary activity to be undertaken to enhance the number and quality of dispensing (pharmacy) capacities in developing countries. In many cases products are being made available through local shops and markets. This is better than no distribution at all, but given the need for appropriate use of drugs to ensure cure and to limit drug resistance, more effort needs to be directed towards distribution mechanisms, dispensing capacity and regulatory oversight.

Appropriate downstream research – implementation research – needs to be undertaken to optimize product use and provide evidence for policy

As well as ensuring adequate research to feed into product R&D, there is equally a need to ensure that adequate research is done on products as they become registered so that evidence is generated for optimal use and policy. This requires a different skill set to product R&D and requires a deeper understanding of health-care systems. As new products come through PPPs we can learn from past TDR experiences in this area; for example, ivermectin for onchocerciasis, praziquantel for schistosomiasis, and more recently Lapdap for malaria and miltefosine for visceral leishmaniasis. Each of these cases is slightly different, but what has been common is a fairly smooth transition from product development and regulatory approval into exploration of optimal use and the provision of evidence for policy. This has came about because of a strong public sector and intergovernmental engagement in ensuring that appropriate research was undertaken and in ensuring the implementation of research output.

Conflicts of interest should be minimized

With the increased sums of funding involved there is a need to ensure that selection, monitoring and review of projects are carried out as objectively as possible and that those undertaking the projects are not involved in any way in the selection and review of their own work. In order to minimize any perceived and real financial and other conflicts, strict rules should be enforced about declarations of interest.

Capacity building and capacity utilization in developing countries should be integrated into product R&D activities

In order to develop a truly sustainable system whereby new products are effectively discovered, developed and implemented, it is important that appropriate capacities in developing countries are both developed and utilized. A sense of local ownership of data and products greatly assists and improves the ability of countries to implement new tools, methodologies and policies. In addition, the expansion of research capabilities and the generation of an appropriate research-based culture in countries results in far better understanding of the options available for policy and hence better decisions on how and what to implement. For example, for product R&D projects, the utilization of developing country investigators, especially for clinical studies, can be extremely useful in ensuring that expertise in best practices are built into country capacities in a sustainable manner. TDR and others have placed great emphasis in recent years on enhancing good clinical practice (GCP) training and facilitating the development of capacity for ethical review within the context of all their product development activities.

There should be strong stakeholdership from developing countries within the context of product R&D, product use and product delivery

Product R&D is often about speed and technical excellence. This is sometimes interpreted to mean that using developing country expertise or 'building research capacity on the job' is a 'nice to have' add-on that can be ignored in the interest of getting a rapid regulatory approval. This is further exacerbated by the fact that almost all donor organizations are from the North and many of the initial recipients of their funds are based in technical, university and industrial institutions in the North. These individuals, even if they have experience of developing country environments, may fail to understand the long-term value and indeed the social responsibility to engage equally with southern partners and to work to ensure that once a project is completed that there is a sustained residual capacity left behind to undertake similar work in the future. Part of this omission occurs, I think, because those involved in the projects view regulatory approval as the end goal. That may be the limit of their responsibility, but it is not why the funding has been given, nor the true goal of the projects. That goal is reached when the products are used and understood by the consumers, and are put into use within national health systems, whether within the private or the public sector. To ensure this occurs rapidly and effectively, the participation of developing country scientists and institutions as equal partners in development teams is essential. There are thankfully many examples within current portfolios where scientists and institutions from developing countries are playing the lead role. However, there is a long way to go to bring any real semblance of parity in this area. If developing countries genuinely believe they are true stakeholders then they may also be inclined to contribute more themselves to product R&D projects and organizations, through both financial and in-kind resources.

Concluding remarks

We have come a long way very quickly in the area of product R&D for diseases of poverty and this progress deserves to be recognized. It should also be recognized that this is due to the financial contributions of a limited number of public sector and philanthropic donor organizations and in-kind contributions from a limited number of pharmaceutical companies. Both of these contributions and the human capital and personal commitment of many individuals engaged in PPPs at the scientific and technical level should be equally valued.

Much of this paper has presented the big picture and has looked at product R&D for diseases of poverty as a whole. However, within the indications that are of interest, we should recognize that there remains a great disparity between areas of major expenditure and global impact (HIV/AIDS, TB, malaria, reproductive health) and others of lesser expenditure and more regional impact (e.g. dengue, schistosomiasis, filariasis, kinetoplastid diseases). A person infected with one of these latter diseases is just as important as one infected with the major diseases and from a human rights and equity perspective, and as a social imperative, these diseases should not be left out of the PPP equation and deserve further prominence.

Finally, we are operating in a new environment with many new players on the stage of product R&D for diseases of poverty. As a community we need to work closely together to ensure that we obtain maximum benefit from this increased array of activities. We need to ensure that pipelines are maintained through enhanced translational research and that new products, once registered, are optimally evaluated and used. As an integral part of a successful strategy we need to ensure we work on the diseases of interest in a manner that is sustainable and builds and utilizes research and other capacities in developing countries.

ANNEX 10

Donor consultation on policy and programming for PD PPPs[1]

Katherine White

Executive summary

The consultation was attended by:

Amie Batson	World Bank
Ted Bianco	Wellcome Trust
Ruairi Brugha	Development Cooperation Ireland
Denis Carroll	USAID
Charles A. Gardner	Rockefeller Foundation
Jane Haycock	UK DFID
Arnd Hoeveler	European Commission, Directorate General for Research
Hannah E. Kettler	Bill & Melinda Gates Foundation
John La Montagne	NIH
Jacques Laruelle	Belgium
Daniel Maeusezahl	Swiss Agency for Development and Cooperation
Ole F. Olesen	European Commission, Directorate General for Research
Ariel Pablos-Mendez	Rockefeller Foundation
Sue Perl	Consultant, Rockefeller Foundation
Paul Spray	UK DFID, *Moderator*
Katalijne van Diest	EDCTP
Harry Van Schooten	Netherlands
Katherine White	Consultant, *Rapporteur*

Garry Aslanyan (Canadian International Development Agency) and Sigrun Møgedal (Norwegian Agency for Development Cooperation) were unable to attend.

[1] Convened in association with the IPPPH workshop: Combating diseases associated with poverty: Financing strategies for product development and the potential role of public-private partnerships.

Main agenda items

- Key takeaways and open questions from the IPPPH's financing strategies meeting.
- Potential areas for coordination and/or further research by the current group of funders.

Meeting summary

The group on the whole agreed that the PD PPPs can be thought of as a coherent field, albeit with broad differences driven by the context in which they operate. There was also clear recognition of the scale of the current funding gap and the urgent need to explore opportunities to increase the efficiency of supporting the existing field, for both funders and the PD PPPs. Primary levers explored were:

- expansion of the current funding base;
- implementation of consistent/comparable performance measures, and ongoing performance management based on these; and
- increasing coordination across funders and between PD PPPs to avoid redundancy.

The discussion covered a number of areas surrounding the current understanding of the PD PPP field and its future needs. The main themes of this discussion are summarized in the detailed notes.

Areas for further exploration/additional work

A wide range of topics were discussed as potential future work that the assembled group could commission. There was, however, no discussion of priority amongst these topics, which included:

- Landscape of current and potential fudners: who are they, what is their focus, do they have any constraints?

- Expanded/complete costing analysis for the PD PPP field to enable a comprehensive assessment of the potential funding gap (based on the initial background paper by Adrian Towse, Jorge Mestre-Ferrandiz and Olwen Renowden, see Annex 9a).
- Mapping of how individual PD PPPs relate or could relate to existing global partnerships (e.g. Global Alliance for TB Drug Development, Roll Back Malaria, Global Fund to Fight AIDS, Tuberculosis and Malaria).
- Framework of potential performance metrics for PD PPP outputs and/or governance issues.
- Assessment of PD PPP potential for future delivery of public health impacts (may also be beneficial to map PD PPP impact on Millennium Development Goals (MDGs) or other commonly agreed public health targets).
- Assessment of donor coordination opportunities (e.g. existing information/resources on the field, regulatory harmonization, advocacy for the field, performance management of PD PPPs) and vehicles for collaboration.

Next steps

- Distribute meeting materials and list of participants to meeting attendees and invitees.
- Hold follow up conference call (all invited) to determine how to move forward and which areas to explore further.
- Publish summary of donor meeting discussion and outcome for distribution with main meeting summary.

Detailed discussion by theme

PD PPP model

There was general agreement that the PD PPPs are a coherent field and that the model is a sound approach to bridge the gap that has existed between blue-sky research and the development of new products for neglected diseases. The field is generally characterized by:

- focus on product development; and
- utilization of the principles for the private sector model for drug development including portfolio management and ensuring communication along the R&D access continuum.

However, there was also recognition of the wide differences in approach across PD PPPs as a result of:

- nuances in product development between devices, drugs, microbicides and vaccines;
- extent of portfolio model implementation; and
- context in which the PD PPP is operating.

For some donors the PD PPP model offers more than increased product development effectiveness. They see PD PPPs as helping to raise awareness regarding neglected diseases and the need for investment in R&D. The challenge for the field in moving forward is to communicate the core strengths and perceived benefits of the model with simple messages that cut across the current field of PD PPPs.

Different views were expressed about future growth of the PD PPP field: some saw increasing proliferation of the PPP model across this and other fields; others believed that the most important opportunities are taken (i.e. greatest social demand and scientific need).

Open questions

- Do we have the right members of the field across PD PPPs and/or within a disease area (are there gaps and/or overlap)?
- Should we also be considering access PPPs with this field or separately?
- What benefits are the PD PPPs delivering today? How does the current set of PPPs stack up relative to the MDGs?
- How do we balance the need to invest in PD PPPs with other approaches to product development?
- How do we balance the need to invest in product development and other parts of the R&D to access continuum?
- How do we balance the need to work with existing tools with the development and delivery of new tools?

Role of PD PPPs within their field

Product development may be the core focus of PD PPPs but many of them are also operating to greater degrees both upstream (translation from basic research) and downstream (ensuring delivery and use of product once delivered). The exact balance between focusing on product development and filling the necessary gaps on the continuum is not clear. However, donors

do not expect PD PPPs to take direct responsibility for establishing delivery systems or basic research programmes. If the end goal of increased public health is to be achieved, they will need to play a role in articulating the needs across the spectrum when gaps are identified.

Open questions

- What role can donors play in mobilizing required resources to ensure delivery systems are in place?
- What is the right balance between getting the product development done and ensuring upstream and downstream gaps are filled?

Interfaces

A large part of the drug development process involves ensuring the correct communication between various different constituents during the process. There was general recognition that in some fields there are still gaps in the links along the R&D to Access continuum. In some disease areas there was concern that more might need to be done to ensure effective 'translation' of basic research ideas into high potential candidates for development.

There was also common agreement that ensuring strong participation from the disease endemic countries early in the development process would be crucial for ensuring usable end products for which there will be demand. It was suggested that there might be opportunities to increase links with the disease-endemic countries (DECs) beyond involvement in access issues and still maintain efficiency of the PPPs (e.g., basic research).

Two particular groups were identified as offering the PPPs additional benefits though their increased involvement in the drug development process: private drug development companies and the DECs for which the drugs are being developed.

Open questions

- How do we ensure strong links between the PD PPPs and different sources of research in their field? Are there opportunities to strengthen links with research in DECs?
- How strong are the current links to DECs and PD PPPs? Is there an opportunity to increase the communication about existing links?
- Can we expand industry involvement from just learning from their models to more direct involvement?

Metrics

While many of the PD PPPs have business plans and metrics available, there does not appear to be a set of commonly understood metrics across the field. There was also recognition of the importance for the field that action be taken based on the metrics to reinforce the management rigour associated with the PPP model.

Two sets of metrics would be required: operating metrics to measure internal performance and output metrics to quantify potential public health impacts. Clear metrics for the field could benefit the PD PPPs by communicating their performance beyond the current audience. In addition the cost of assessment and monitoring for both donors and PD PPPs will become substantial without common metrics. For donors, in particular, there is a strong desire to have output metrics for the field that allow them to compare investment in PD PPPs with other types of investment.

Open questions

- What operational metrics are applied by PD PPPs today? What works?
- Is there a way to quantify both social demand and scientific maturity to enable comparison across the PD PPP field and existing tools(e.g., actuarial methods)?
- Can products be mapped against MDGs with a reasonable amount of effort?
- When things are failing should someone go in and 'fix it' (i.e., the fire the CEO/board model) or should the operation be shut down?
- Are donors willing to be disciplined and withhold funds when performance justifies it?

Funding

There was strong agreement about the severity of the funding gap and concerns that the current funding base is not sufficient to sustain existing field. There was also a strong desire to have a clearer picture of the true funding gap (expanding on the background paper prepared for the main meeting, *see* Annex 9a).

The group agreed that broadening the funding base beyond traditional 'development' funders would re-

quire a focused advocacy effort if PD PPPs were to reach a wider group (e.g. not all G8 involved today). On top of this, there is growing concern that the PPP field (not just PD PPPs) is stretching the bandwidth of human resources of both existing funders and the PPPs because of the time spent educating and lobbying. A number of potential strategies were discussed, e.g., a letter to the G8 signed by existing supporters. In general it was agreed that none of these strategies would be successful without clear, simple messages about the benefits and public health outcomes the PD PPPs could deliver. At the same time the group recognized that PD PPPs are not the only product development model.

Open questions

- What is the true funding gap?
- Who are potential donors and what constraints/goals influence what they can fund?
- What role can existing funders play to help attract additional funders?
- What is the right funding balance between PD PPPs and other product development models?

Advocacy

The group also believed that donors will need to expand their role beyond the provision of funds. There could be benefit from donors working together to advocate for additional support and an expanded donor base. Donors could also collaborate with existing stakeholders on issues such as regulatory harmonization and delivery systems.

Advocacy for the PPP model would need to include why we believe in them, their benefits and desired end points. A common advocacy effort would have the additional benefits of increasing credibility of the PD PPPs as well as potentially broadening the funding base.

Open questions

- Could the MDGs be used to help support a common advocacy message (e.g., PPPs mapped to MDGs or analysis that we won't meet MDGs and highlighting what new technologies could bring)?
- How can the resources of access PPPs be leveraged to help with some of the broader advocacy issues? Do all PPPs have appropriate access PPPs to support them?
- Could the role of advocacy for the PD PPP field be better achieved through a coordinated effort (i.e., donors or PD PPPs, or both)?
- Should advocacy (for the end use of the product) be delegated to an access PPP or other entity?

Coordination

There was strong agreement that as the field grows, it would benefit from increased coordination among the donors and the PD PPPs. Representatives of PD PPPs present at the meeting strongly believed that this would need to be driven by the PD PPPs themselves. Amongst the donor group, there was a belief that at minimum donors could benefit from a quasi-regular sharing of information (e.g., assessments/studies completed).

Open questions

- What resources are available to share across donors? Are donors already duplicating effort?
- Are there opportunities to work together on new work to be completed (e.g., independent assessments)?
- Are there common frameworks for proposals, etc. (e.g., GAVI investment framework) that could reduce transaction costs for PPPs and donors?

Topics raised but not discussed

- Product liability
- Intellectual property

ANNEX 11

Consolidation of the private partnership for product development: Africa's role[1]

Ebi Kimanani, with contributions from Bartholomew Dicky Akanmori, Karniyus Shingu Gamaniel, Uford Samson Inyang, John Kilama, Andrew Kitua, Rose Leke and Kisali Pallangyo

Executive summary

The public-private partnership (PPP) model for developing products for diseases of poverty is now well beyond the experimental stage and needs to be consolidated by including some core issues pertinent to its challenging mission. In the meeting organized by the Initiative on Public-Private Partnerships for Health (IPPPH),[2] participants repeatedly noted that in order for the PPP model to be complete, it is essential to have broader core representation from the various constituencies of Africa and other regions of interest. The parameters of this partnership component need to be defined primarily by such representatives in collaboration with other key players. The seven co-authors of this paper cover much of the sub-Saharan region, including western and eastern, francophone and anglophone Africa. We also represent a wide range of disciplines and research profiles in Africa, such as traditional medicine, industry, contract research organizations, national research institutes, academic medical institutions and research networks. We would, therefore, like to spearhead the process of defining a consolidated platform for partnership in the product development (PD) PPP model that will add value to the current efforts of these PPPs and address important needs of African communities. We shall start this process by responding to the six key questions arising from the IPPPH meeting, from the perspectives of our various sub-constituencies, expertise, national governments and communities. At the same time as we dialogue with PD PPPs, we shall approach the African Health Research Forum (AfHRF) and other regional and international forums in order to engage a continent-wide consortium in the affirmation of African researchers' role in global product development.

Three key areas that we would like to bring to the PD PPP platform as components of an African partnership are clinical trial facilitation, research and development of African traditional medicines and the institution of an African scientific and technical review committee.

'Is there a role for investment in systemic issues?' was one of the questions that arose during the meeting. We feel that the answer to this question is yes, through the facilitation of clinical trials,[3] and we suggest how to proceed. Paralleling the concerted activities of PD PPPs, African product development is a grass-roots innovative effort that builds upon existing health-care practices using products that are familiar and accessible to the vast majority of communities in Africa. This should be taken as a credible alternative approach that could benefit from the methods used by PD PPPs for fundraising, project planning and management. The component on a regional technical review committee is an essential support action for all clinical research activities on the continent. Since the issue of ethics is fundamentally about linking the clinical research culture to study participant communities, we would like to play a role in defining some of the best practices that should be in place.

[1] Prepared in response to the workshop on: Combating diseases associated with poverty: Financing strategies for product development and the potential role of public-private partnerships.

[2] Combating diseases associated with poverty: Financing strategies for product development and the potential role of public-private partnerships, Wellcome Trust, UK, April 15–16.

[3] An operational plan for such facilitation has been prepared and is available for anyone who wishes to discuss this concept further and can be accessed through the IPPPH.

Clinical trial facilitation

Coordinator: Dr. Ebi Kimanani

There is a need for a Compared to other components of PD PPPs, the facilitation of clinical trials requires relatively low initial investment and has many components that do not require high-tech expertise. In addition, with the right kind of targeted training and system development, clinical trials could be handled by personnel trained and living in Africa. We therefore feel that a core part of clinical trial facilitation should be handled by Africans through African institutions and that this is a viable starting point to develop some of the systemic issues across PD PPPs. This can be handled through a research organization whose main focus would be site assessment, management, coordination and general facilitation of clinical studies in Africa. In the long run, such an organization would become a centre of excellence for clinical trials in sub-Saharan Africa. The goals of such an entity are listed below.

Goals

- To provide a link in the present chain of drug development in which funders and product developers are primarily in the North and the patients are in Africa.
- To ensure that regions in Africa play a viable and sustainable role in clinical trials.
- To provide an opportunity for African data ownership.
- To play a leading role in creating guidelines to harmonize good clinical practice through the region.
- T set achievable targets for local capacity.
- To develop and update an investigator/site database for clinical trials in Africa with a capacity assessment component.
- Develop a database of Institutional Review Boards or Ethical Review Committees and their adherence to WHO guidelines.

Importance of collaborations of African scientific leaders

Key challenges in creating such an organization (RO) in Africa include:

- Sites are located in different countries with different regulations, research and socio-economic cultures and levels of poverty. The ease with which one can work in these multiple sites therefore depends on the political and economical relationship between the countries. Of particular challenge will be how to work with possibly dissimilar and fragmented regulations.
- At present, functioning sites are national research institutions, each of which is mandated to serve the country not the region. The RO must respect and integrate the sites' independence into its mission and find a creative way to organize regionally and execute nationally.
- Many of those sites are located in some of the least economically developed regions in the world and bring with them the clinical care and research challenges inherent in such resource-deprived settings.

Hence the support pledged to this cause by the seven leading African participants at the IPPPH meeting is a critical element of success.

A partnership foundation

This research organization will be more than just a loose affiliation with research sites. It must be a direct and indirect partnership with various constituencies involved in clinical research in Africa. These include the patient, investigator site or clinical centre, governments and other regulatory authorities in each country, product developers, funding agencies and other clinical trial sponsors. The foundation of this RO must acknowledge, interpret and consolidate the different cultures and expectations that each of these stakeholders bring to the partnership. In order to do this effectively, the governance structure must legitimately represent these constituencies. It must also be accountable and competent. Emphasis should be placed on lean, well defined, accountable and transparent governance and management structures that will be allowed to evolve as experience is gained. Starting with the sites represented by the co-authors, sites will be recruited on a voluntary basis through memoranda of understanding based on the following guiding principles:

- Respect for the separate missions of each site.
- Assured flexible association that allows the sites to work with other sponsors, networks and other research initiatives.
- Common strategy through operating procedures, information technology systems, etc.

- Transparent certification criteria regarding the level of readiness for clinical trials.
- Credible and sustainable training and capacity-building systems that benefit all sites.
- Articulated expectations within and between the various partners.

Reception of the RO model by drug developers

Drug development offers the following challenge: expertise for developing drug products rests overwhelmingly in the commercial world; while the health problems of developing countries exist in a different, almost independent, and in this case African, world. Until recently, there was no tangible link between these two worlds. PD PPPs were formed as a way to bridge this gap by offering incentives through the sharing of costs and other resources. This proposed African RO fits in very well with this thinking, i.e., a partnership formed to bridge the clinical trial facilitation gap between Northern product developers and funding agencies, and African research sites and investigators. In this model, the required cost and other input resources that go into each unit of capacity development will be estimated. Potential end users will be approached to identify which clinical trial service they will utilize and be requested to contribute to the development of the capacities that go along with it. This contribution will be either financial or in-kind support depending on the input resource requirements. We believe that this mutual investment of resources is a more efficient and cost-effective approach for the following reasons:

- Up-front costs will be shared among many sponsors with similar interests.
- Each potential site will interact with one organization, thus avoiding duplication of processes.
- Potential site competition will be avoided.
- Negotiations for partnerships will be based on this model. Examples of hypothetical partnership agreements are given in Appendix 1.

It is our view that an African research organization, which aims to assess, manage and coordinate sites during clinical trials, is a specific, feasible and meaningful contribution from African players in the PD PPPs. In addition it is a cost-effective opportunity to invest in systemic issues that cut across PPPs.

Traditional medicines

Coordinators: Prof. Karniyus Gamaniel, Dr. Uford Inyang, Prof. Kisali Pallangyo

In many countries in Africa, the ratio of orthodox medical practitioners to the general population is about 1:2000 while that for traditional health practitioners has been estimated at 1:200. Traditional African medicines (TAMs) are thus accessible, affordable, available and acceptable to Africans. TAMs need to be developed through standardization, safety and clinical evaluations, registration, marketing and official recognition with appropriate structures for regulating the quality of TAM products. In addition to these usual challenges to drug discovery and development, searching for and harvesting the candidate plants have to be approached in an environmentally sensitive and sustainable manner. The appropriate development of TAMs poses a challenge to many governments in Africa, which nonetheless appreciate the importance of traditional approaches to health care. The Nigerian government set up the National Institute of Pharmaceutical Research and Development (NIPRD) exclusively to harness, discover and develop TAMs. Cameroon's Institute of Medical Research and Studies of Medicinal Plants (IMPM) and the Institute of Traditional Medicine in Tanzania are other examples of the recognition of the importance of this approach by governments in the region. We would like to consider the extent to which the experiences and operational procedures of PD PPPs can be applied to the development of TAMs with a view to fostering research and manufacturing partnerships.

Examples of activities to be initiated

- Continent-wide inventory of the numerous plant species with potential for medicinal uses.
- Standardization of research methods.
- Development and harmonization of regulatory and ethical requirements.
- Advocacy and awareness campaigns.
- Education of international community.

Importance of collaborations between African scientific leaders

In order to institute sustainable TAM practices, the abovementioned goals can only be meaningfully addressed by scientific partnerships in all sub-regions of the continent. Given that the African participants to

the IPPPH meeting span western and eastern Africa, orthodox and traditional medicines, and clinical research including product development, their endorsement of this initiative is critical for placing TAM on the PD PPP agenda.

African scientific and technical review committee

Coordinator: Prof. Rose Leke

To date, the prevailing wisdom has been to make clinical trial applications for phase I trials through regulatory authorities in the United States and Europe, and then to go ahead with phase II and higher trials at the developing country site. A prerequisite for these sites has been the establishment of IRBs and training of their members so that they will be able to review the ethical aspects of the trial for the developing country trial site, and to monitor its progress to ensure compliance with good clinical practice. In some cases these IRBs have been accredited by the US National Institutes of Health. This work is important and basic, and must continue. The big problem with this approach is that it is completely driven from the outside. Since the issue of ethics is where science meets the people, we feel that in the case of African communities, the primary link should be by individuals who have their roots in the African village or community and have had sufficient exposure to science, clinical research and other cultures, especially Western culture. Such individuals are conversant with both cultures in fundamental ways that go beyond language alone and have credibility in – and hence are accountable to – both communities.

We would like to do this within the International Scientific and Technical Review Committee (ISTARC) which is being facilitated by Dr. Julie Milstien of WHO.

APPENDIX 1. HYPOTHETICAL EXAMPLES OF THE APPLICATION OF THE PARTNERSHIP MODEL

Project	Sponsor	RO's responsibility	Sponsor's responsibility	Research team	Physical facilities	Sponsor's contribution
Phase III **HIV** microbicide trial. Effectiveness, placebo-controlled, 2000 participants, four-year study.	International research organization, **PPP**	Site and investigator recruitment; regulatory requirements; ethical submission; informed consent; community outreach; subject recruitment and follow-up; drug importation, storage and dispensing; adverse event reporting; project management; data collection and entry.	GLP and GCP training; purchase all equipment for the study including lab, computer hardware and communication; renovate study facility including lab and subject interview and examination rooms. Allow one year preparatory period.	Principal investigator; two co-investigators; one research coordinator; four study nurses; three lab technicians; four field assistants; one HIV/AIDS counsellor; one administrative assistant; one accountant; three auxiliary staff.	Examination rooms; laboratory; drug storage; document storage and archiving; administrative space.	**40% to overall phase I budget**
Phase II/III efficacy, two-arm, standard therapy comparator, 300 **malaria** patients, six-month study.	Pharma company, **Industry**	Clinical monitoring; regulatory affairs; ethical review submission; site identification and management; drug importation, dispensing and accountability; project management.	GCP training; purchase essential lab equipment; communication and computer hardware.	One project manager; one research coordinator; three study nurses; three monitors; three field assistants; one administrative assistant; one accountant; three auxiliary staff.	Storage; administrative space.	**7.5%**
Phase III **HIV** microbicide trial. Effectiveness, placebo-controlled, 250 participants, two-year study.	International research organization, **PPP**	Principal investigators; regulatory requirements; ethical submission; informed consent; community outreach; subject recruitment and follow-up; drug importation, storage and dispensing; adverse event reporting; project management; data collection and entry.	GLP and GCP training; purchase all equipment for the study including lab, computer hardware and communication; renovate study facility including lab and subject interview and examination rooms.	Principal investigator; one research coordinator; two study nurses; two lab technicians; two field assistants; one HIV/AIDS counsellor; one administrative assistant; one accountant; two auxiliary staff.	Examination rooms; laboratory; drug storage; document storage and archiving; administrative space.	**10%**

APPENDIX 2. EXAMPLES OF SERVICES AND CAPACITIES

Services	Required human resources
DATA MANAGEMENT	
• Design, handling and storage of case report forms • Database design • Medical coding • Data entry and verification • Quality control/assurance • Internet data collection	• Database programmers sensitive to regulatory requirements • Data entry clerks • Record and data archivists • Quality control/assurance professionals
BIOMETRICS AND EPIDEMIOLOGY	
• Protocol development • Study design • Sample size estimation • Statistical analysis plans • Data analysis/statistical and other reports • Epidemiological studies	• Statistical programmers • Biostatisticians • Epidemiologists • Medical writers
SITE ASSESSMENT AND MANAGEMENT	
• Site identification: facilities, staff • Research staff qualification • Investigators' meetings • Project tracking • Essential documents • Site auditing • Regulatory guidelines • Ethical review procedures • Level of readiness for clinical trials	• Clinical research associates • Regulatory personnel • Quality control/assurance professionals • Project managers • Documentation specialists
INVESTIGATOR SITE DATABASE	
• Site location and access using GIS[1] • Investigator biodata and research experience • Estimated prevalence of disease	• Database designers and programmers • GIS experts

[1] GIS = Geographic Information Systems

The aim of the Initiative on Public-Private Partnerships for Health is to increase the effectiveness of public-private collaboration, particularly by helping those seeking to develop health products, or to improve access to such products needed to fight neglected diseases and other health problems in developing countries.

Created in 2000 in Geneva, Switzerland, the Initiative on Public-Private Partnerships for Health is sponsored by the Bill & Melinda Gates Foundation, the Rockefeller Foundation and the World Bank. It operates under the aegis of the Global Forum for Health Research, an independent international foundation helping to correct the 10/90 gap in health research, from which it also receives support (www.globalforumhealth.org).

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